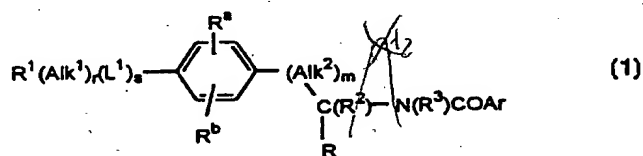




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<p>(21) International Application Number: PCT/GB99/00589</p> <p>(22) International Filing Date: 26 February 1999 (26.02.99)</p> <p>(30) Priority Data: 9804161.9 26 February 1998 (26.02.98) GB 9826668.7 3 December 1998 (03.12.98) GB</p> <p>(71) Applicant (for all designated States except US): CELLTECH THERAPEUTICS LIMITED [GB/GB]; 216 Bath Road, Slough, Berkshire SL1 4EN (GB).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): ARCHIBALD, Sarah, Catherine [GB/GB]; 5 College Glen, Maidenhead, Berkshire SL6 6BL (GB). HEAD, John, Clifford [GB/GB]; 4 Dorchester Close, Maidenhead, Berkshire SL6 6RX (GB). WARRELOW, Graham, John [GB/GB]; Oakside, 4 Wieland Road, Northwood, Middlesex HA6 3QU (GB). PORTER, John, Robert [GB/GB]; 7 Farm Place, Henton, Chinnor, Oxfordshire OX9 4AD (GB).</p> <p>(74) Agents: MERCER, Christopher, Paul et al.; Carpmals & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	

(54) Title: PHENYLALANINE DERIVATIVES AS INHIBITORS OF ALPHA4 INTEGRINS



(57) Abstract

Phenylalanine derivatives of formula (1) are described: wherein R is a carboxylic acid or a derivative thereof; L¹ is a linker atom or group; Ar is an optionally substituted aromatic group; and the salts, solvates, hydrates and N-oxides thereof. The compounds are able to inhibit the binding of alpha4 integrins to their ligands and are of use in the prophylaxis and treatment of immune or inflammatory disorders.

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PHENYLALANINE DERIVATIVES AS INHIBITORS OF ALPHA4 INTEGRINS

5 This invention relates to a series of phenylalanine derivatives, to compositions containing them, to processes for their preparation, and to their use in medicine.

Over the last few years it has become increasingly clear that the physical interaction of inflammatory leukocytes with each other and other cells of the body plays an important role in regulating immune and inflammatory responses [Springer, T. A. *Nature*, 346, 425, (1990); Springer, T. A. *Cell* 76, 301, (1994)]. Many of these interactions are mediated by specific cell surface molecules collectively referred to as cell adhesion molecules.

15 The adhesion molecules have been sub-divided into different groups on the basis of their structure. One family of adhesion molecules which is believed to play a particularly important role in regulating immune and inflammatory responses is the integrin family. This family of cell surface glycoproteins has a typical non-covalently linked heterodimer structure. At least 14 different integrin alpha chains and 8 different integrin beta chains have been identified [Sonnenberg, A. *Current Topics in Microbiology and Immunology*, 184, 7, (1993)]. The members of the family are typically named according to their heterodimer composition although trivial nomenclature is widespread in this field. Thus the integrin termed $\alpha_4\beta_1$ consists of the integrin alpha 4 chain associated with the integrin beta 1 chain, but is also widely referred to as Very Late Antigen 4 or VLA4. Not all of the potential pairings of integrin alpha and beta chains have yet been observed in nature and the integrin family has been subdivided into a number of subgroups based on the pairings that have been recognised [Sonnenberg, A. *ibid*].

The importance of cell adhesion molecules in human leukocyte function has been further highlighted by a genetic deficiency disease called Leukocyte Adhesion Deficiency (LAD) in which one of the families of leukocyte integrins is not expressed [Marlin, S. D. *et al* *J. Exp. Med.* 164, 855 (1986)]. Patients with this disease have a reduced ability to recruit

leukocytes to inflammatory sites and suffer recurrent infections which in extreme cases may be fatal.

5 The potential to modify adhesion molecule function in such a way as to beneficially modulate immune and inflammatory responses has been extensively investigated in animal models using specific monoclonal antibodies that block various functions of these molecules [e.g. Issekutz, T. B. J. Immunol. 3394, (1992); Li, Z. *et al* Am. J. Physiol. 263, L723, (1992); Binns, R. M. *et al* J. Immunol. 157, 4094, (1996)]. A number of
10 monoclonal antibodies which block adhesion molecule function are currently being investigated for their therapeutic potential in human disease.

One particular integrin subgroup of interest involves the α_4 chain which
15 can pair with two different beta chains β_1 and β_7 [Sonnenberg, A. *ibid*]. The $\alpha_4\beta_1$ pairing occurs on many circulating leukocytes (for example lymphocytes, monocytes and eosinophils) although it is absent or only present at low levels on circulating neutrophils. $\alpha_4\beta_1$ binds to an adhesion molecule (Vascular Cell Adhesion Molecule-1 also known as VCAM-1)
20 frequently up-regulated on endothelial cells at sites of inflammation [Osborne, L. Cell, 62, 3, (1990)]. The molecule has also been shown to bind to at least three sites in the matrix molecule fibronectin [Humphries, M. J. *et al*. Ciba Foundation Symposium, 189, 177, (1995)]. Based on data obtained with monoclonal antibodies in animal models it is believed
25 that the interaction between $\alpha_4\beta_1$ and ligands on other cells and the extracellular matrix plays an important role in leukocyte migration and activation [Yednock, T. A. *et al*, Nature, 356, 63, (1992); Podolsky, D. K. *et al*. J. Clin. Invest. 92, 373, (1993); Abraham, W. M. *et al*. J. Clin. Invest. 93, 776, (1994)].

30 The integrin generated by the pairing of α_4 and β_7 has been termed LPAM-1 [Holzmann, B and Weissman, I. EMBO J. 8, 1735, (1989)] and like $\alpha_4\beta_1$, binds to VCAM-1 and fibronectin. In addition, $\alpha_4\beta_7$ binds to an adhesion molecule believed to be involved in the homing of leukocytes to
35 mucosal tissue termed MAdCAM-1 [Berlin, C. *et al*, Cell, 74, 185, (1993)]. The interaction between $\alpha_4\beta_7$ and MAdCAM-1 may also be important at

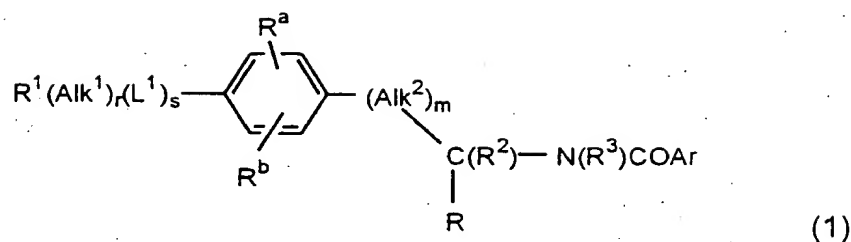
sites of inflammation outside of mucosal tissue [Yang, X-D. *et al*, PNAS, 91, 12604 (1994)].

Regions of the peptide sequence recognised by $\alpha_4\beta_1$ and $\alpha_4\beta_7$ when they
5 bind to their ligands have been identified. $\alpha_4\beta_1$ seems to recognise LDV,
IDA or REDV peptide sequences in fibronectin and a QIDSP sequence in
VCAM-1 [Humphries, M. J. *et al*, *ibid*] whilst $\alpha_4\beta_7$ recognises a LDT
sequence in MAdCAM-1 [Briskin, M. J. *et al*, J. Immunol. 156, 719,
(1996)]. There have been several reports of inhibitors of these interactions
10 being designed from modifications of these short peptide sequences
[Cardarelli, P. M. *et al* J. Biol. Chem. 269, 18668, (1994); Shroff, H. N.
Bioorganic. Med. Chem. Lett. 6, 2495, (1996); Vanderslice, P. J. Immunol.
158, 1710, (1997)]. It has also been reported that a short peptide
sequence derived from the $\alpha_4\beta_1$ binding site in fibronectin can inhibit a
15 contact hypersensitivity reaction in a trinitrochlorobenzene sensitised
mouse [Ferguson, T. A. *et al*, PNAS 88, 8072, (1991)].

Since the alpha 4 subgroup of integrins are predominantly expressed on
leukocytes their inhibition can be expected to be beneficial in a number of
20 immune or inflammatory disease states. However, because of the
ubiquitous distribution and wide range of functions performed by other
members of the integrin family it is very important to be able to identify
selective inhibitors of the alpha 4 subgroup.

25 We have now found a group of compounds which are potent and selective
inhibitors of α_4 integrins. Members of the group are able to inhibit α_4
integrins such as $\alpha_4\beta_1$ and/or $\alpha_4\beta_7$ at concentrations at which they
generally have no or minimal inhibitory action on α integrins of other
subgroups. The compounds are thus of use in medicine, for example in
30 the prophylaxis and treatment of immune or inflammatory disorders as
described hereinafter.

Thus according to one aspect of the invention we provide a compound of
formula (1)



wherein

R is a carboxylic acid or a derivative thereof;

5 R¹ is a hydrogen atom or a hydroxyl, straight or branched alkoxy or optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk¹ is an optionally substituted aliphatic or heteroaliphatic chain;

L¹ is a linker atom or group;

10 r and s, which may be the same or different, is each zero or an integer 1 provided that when r is zero R¹ is an optionally substituted cycloaliphatic, polycycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

R^a and R^b, which may be the same or different is each an atom or group

15 -L²(CH₂)_pL³(R^c)_q in which L² and L³ is each a covalent bond or a linker atom or group, p is zero or the integer 1, q is an integer 1, 2 or 3 and R^c is a hydrogen or halogen atom or a group selected from straight or branched alkyl, -OR^d [where R^d is a hydrogen atom or an optionally substituted straight or branched alkyl group], -SR^d, -NR^dR^e, [where R^e is as just defined for R^d and may be the same or different], -NO₂, -CN, -CO₂R^d, -SO₃H, -SO₂R^d, -OCO₂R^d, -CONR^dR^e, -OCONR^dR^e, -CSNR^dR^e, -COR^d, -N(R^d)COR^e, N(R^d)CSR^e, -SO₂N(R^d)(R^e), -N(R^d)SO₂R^e, -N(R^d)CONR^eR^f [where R^f is a hydrogen atom or an optionally substituted straight or branched alkyl group], -N(R^d)CSNR^eR^f or -N(R^d)SO₂NR^eR^f;

25 Alk² is a straight or branched alkylene chain;

m is zero or an integer 1;

R² is a hydrogen atom or a methyl group;

R³ is a hydrogen atom or a straight or branched alkyl group;

Ar is an optionally substituted aromatic group;

30 and the salts, solvates, hydrates and N-oxides thereof, for use in modulating cell adhesion.

The compounds of formula (1) are potent and selective inhibitors of α_4 integrins. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter. In particular compounds of the invention are advantageously selective $\alpha_4\beta_1$ inhibitors

The compounds of formula (1) are thus of use in modulating cell adhesion and in particular are of use in the prophylaxis and treatment of diseases or disorders involving inflammation in which the extravasation of leukocytes plays a role. The invention extends to such a use and to the use of compounds of formula (1) for the manufacture of a medicament for treating such diseases or disorders. Diseases or disorders of this type include inflammatory arthritis such as rheumatoid arthritis vasculitis or polydermatomyositis, multiple sclerosis, allograft rejection, diabetes, inflammatory dermatoses such as psoriasis or dermatitis, asthma and inflammatory bowel disease.

For the prophylaxis or treatment of disease the compounds of formula (1) may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents, for use in modulating cell adhesion, particularly in the prophylaxis and treatment of diseases or disorders involving inflammation as just described.

Pharmaceutical compositions for use according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation and the invention extends to the use of a compound of formula (1) in the manufacture of such formulations.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or

hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets
5 may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable
10 additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give
15 controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

20 The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or
25 aqueous vehicles, and may contain formulatory agents such as suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

30 In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

35 For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the

form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

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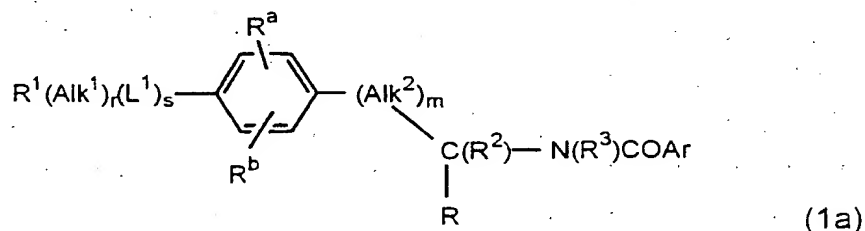
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

10

The quantity of a compound of formula (1) required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, effective daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

20

Particular compounds of formula (1) form a further feature of the invention and in a further aspect we therefore provide a compound of formula (1a):



25

wherein

R is a carboxylic acid or a derivative thereof;

R¹ is an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

30

Alk¹ is an optionally substituted aliphatic or heteroaliphatic chain;

L¹ is a linker atom or group;

- r and s, which may be the same or different, is each zero or an integer 1;
 R^a and R^b , which may be the same or different is each an atom or group
 $-L^2(CH_2)_pL^3(R^c)_q$ in which L^2 and L^3 is each a covalent bond or a linker
atom or group, p is zero or the integer 1, q is an integer 1, 2 or 3 and R^c is
5 a hydrogen or halogen atom or a group selected from straight or branched
alkyl, $-OR^d$ [where R^d is a hydrogen atom or an optionally substituted
straight or branched alkyl group], $-SR^d$, $-NR^dR^e$, [where R^e is as just
defined for R^d and may be the same or different], $-NO_2$, $-CN$, $-CO_2R^d$,
 $-SO_3H$, $-SO_2R^d$, $-OCO_2R^d$, $-CONR^dR^e$, $-OCONR^dR^e$, $-CSNR^dR^e$, $-COR^d$,
10 $-N(R^d)COR^e$, $N(R^d)CSR^e$, $-SO_2N(R^d)(R^e)$, $-N(R^d)SO_2R^e$, $-N(R^d)CONR^eR^f$
[where R^f is a hydrogen atom or an optionally substituted straight or
branched alkyl group], $-N(R^d)CSNR^eR^f$ or $-N(R^d)SO_2NR^eR^f$;
 Alk^2 is a straight or branched alkylene chain;
m is zero or an integer 1;
15 R^2 is a hydrogen atom or a methyl group;
 R^3 is a hydrogen atom or a straight or branched alkyl group;
Ar is an optionally substituted aromatic group;
and the salts, solvates, hydrates and N-oxides thereof.
- 20 It will be appreciated that compounds of formulae (1) and (1a) may have
one or more chiral centres. Where one or more chiral centres is present,
enantiomers or diastereomers may exist, and the invention is to be
understood to extend to all such enantiomers, diastereomers and mixtures
thereof, including racemates. Formulae (1) and (1a) and the formulae
25 hereinafter are intended to represent all individual isomers and mixtures
thereof, unless stated or shown otherwise.

In the compounds of formulae (1) and (1a), derivatives of the carboxylic
acid group R include carboxylic acid esters and amides. Particular esters
30 and amides include $-CO_2Alk^4$ and $-CON(R^4)_2$ groups as described herein.

When in the compounds of formulae (1) and (1a) L^1 is present as a linker
atom or group it may be any divalent linking atom or group. Particular
examples include $-O-$ or $-S-$ atoms or $-C(O)-$, $-C(O)O-$, $-C(S)-$, $-S(O)-$,
35 $-S(O)_2-$, $-N(R^4)-$ [where R^4 is a hydrogen atom or a straight or branched
alkyl group], $-CON(R^4)-$, $-OC(O)N(R^4)-$, $-CSN(R^4)-$, $-N(R^4)CO-$,

-N(R⁴)C(O)O-, -N(R⁴)CS-, -S(O)N(R⁴)-, -S(O)₂N(R⁴)-, -N(R⁴)S(O)-, -N(R⁴)S(O)₂-, -N(R⁴)CON(R⁴)-, -N(R⁴)CSN(R⁴)-, -N(R⁴)SON(R⁴)- or -N(R⁴)SO₂N(R⁴)- groups. Where the linker group contains two R⁴ substituents, these may be the same or different.

5

Alk² in the compounds of formulae (1) and (1a) may be for example a straight or branched C₁₋₃alkylene chain. Particular examples include -CH₂-, -CH(CH₃)-, -C(CH₃)₂- and -(CH₂)₂-.

10. When R³ and/or R⁴ in the compounds of formula (1) is a straight or branched alkyl group it may be a straight or branched C₁₋₆ alkyl group, e.g. a C₁₋₃ alkyl group such as a methyl or ethyl group.

- When Alk¹ in compounds of formula (1) is an optionally substituted aliphatic chain it may be an optionally substituted C₁₋₁₀ aliphatic chain. Particular examples include optionally substituted straight or branched C₁₋₆ alkylene, C₂₋₆ alkenylene, or C₂₋₆ alkynylene chains.
- 15.

- Heteroaliphatic chains represented by Alk¹ include the aliphatic chains just described but with each chain additionally containing one, two, three or four heteroatoms or heteroatom-containing groups. Particular heteroatoms or groups include atoms or groups L⁴ where L⁴ is as defined above for L¹ when L¹ is a linker atom or group. Each L⁴ atom or group may interrupt the aliphatic chain, or may be positioned at its terminal carbon atom to connect the chain to the atom or group R¹.
- 20
- 25

- Particular examples of aliphatic chains represented by Alk¹ include optionally substituted -CH₂-, -CH₂CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -(CH₂)₂CH₂-, -CH(CH₃)CH₂-, -(CH₂)₃CH₂-, -CH(CH₃)CH₂CH₂-, -CH₂CH(CH₃)CH₂-, -C(CH₃)₂CH₂-, -(CH₂)₄CH₂-, -(CH₂)₅CH₂-, -CHCH-, -CHCHCH₂-, -CH₂CHCH-, -CHCHCH₂CH₂-, -CH₂CHCHCH₂-, -(CH₂)₂CHCH-, -CC-, -CCCH₂-, -CH₂CC-, -CCCH₂CH₂-, -CH₂CCCH₂-, or -(CH₂)₂CC- chains. Where appropriate each of said chains may be optionally interrupted by one or two atoms and/or groups L⁴ to form an optionally substituted heteroaliphatic chain. Particular examples include
- 30
- 35

optionally substituted $-L^4CH_2-$, $-CH_2L^4CH_2-$, $-L^4(CH_2)_2-$, $-CH_2L^4(CH_2)_2-$, $-(CH_2)_2L^4CH_2-$, $-L^4(CH_2)_3-$ and $-(CH_2)_2L^4(CH_2)_2-$ chains.

The optional substituents which may be present on aliphatic or heteroaliphatic chains represented by Alk^1 include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C_{1-6} alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6} alkylthio e.g. methylthio or ethylthio, amino or substituted amino groups. Substituted amino groups include $-NHR^4$ and $-N(R^4)_2$ groups where R^4 is a straight or branched alkyl group as defined above. Where two R^4 groups are present these may be the same or different. Particular examples of substituted chains represented by Alk^1 include those specific chains just described substituted by one, two, or three halogen atoms such as fluorine atoms, for example chains of the type $-CH(CF_3)-$, $-C(CF_3)_2-$, $-CH_2CH(CF_3)-$, $-CH_2C(CF_3)_2-$, $-CH(CF_3)-$ and $-C(CF_3)_2CH_2$.

Alkoxy groups represented by R^1 in compounds of formula (1) include straight or branched C_{1-6} alkoxy groups such as methoxy and ethoxy groups.

20

When R^1 is present in compounds of formulae (1) and (1a) as an optionally substituted cycloaliphatic group it may be an optionally substituted C_{3-10} cycloaliphatic group. Particular examples include optionally substituted C_{3-10} cycloalkyl, e.g. C_{3-7} cycloalkyl, C_{3-10} cycloalkenyl e.g. C_{3-7} cycloalkenyl or C_{3-10} cycloalkynyl e.g. C_{3-7} cycloalkynyl groups.

Optionally substituted heterocycloaliphatic groups represented by R^1 include the optionally substituted cycloaliphatic groups just described for R^1 but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups L^2 as just defined.

Optionally substituted polycycloaliphatic groups represented by R^1 include optionally substituted C_{7-10} bi- or tricycloalkyl or C_{7-10} bi- or tricycloalkenyl groups. Optionally substituted polyheterocycloaliphatic groups represented by R^1 include the optionally substituted polycycloalkyl groups

just described, but with each group additionally containing one, two, three or four L² atoms or groups.

Particular examples of R¹ cycloaliphatic, polycycloaliphatic, heterocycloaliphatic and polyheterocycloaliphatic groups include optionally substituted
 5 cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, adamantyl, norbornyl, norbornenyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, pyrrolidinone, oxazolidinyl, oxazolidinone, dioxolanyl, e.g. 1,3-dioxolanyl,
 10 imidazolanyl, e.g. 2-imidazolanyl, imidazolidinyl, pyrazolanyl, e.g. 2-pyrazolanyl, pyrazolidinyl, thiazolanyl, thiazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, piperidinone, 1,4-dioxanyl, morpholanyl, morpholinone, 1,4-dithianyl, thiomorpholanyl, piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl,
 15 isoxazinyl, e.g. o- or p-isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or oxadiazinyl e.g. 1,3,5-oxodiazinyl groups.

The optional substituents which may be present on the R¹ cycloaliphatic, polycycloaliphatic, heterocycloaliphatic or polyheterocycloaliphatic groups
 20 include one, two, three or more substituents represented by R⁵ in which R⁵ is selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl or ethyl, haloC₁₋₆alkyl, e.g. halomethyl or haloethyl such as difluoromethyl or trifluoromethyl, hydroxyl, C₁₋₆alkoxy, e.g. methoxy or ethoxy, haloC₁₋₆alkoxy, e.g. halomethoxy or
 25 haloethoxy such as difluoromethoxy or trifluoromethoxy, thiol, C₁₋₆alkylthio e.g. methylthio or ethylthio, -N(R⁴)₂, -CN, -CO₂R⁴, -NO₂, -CON(R⁴)₂, -CSN(R⁴)₂, -COR⁴, -CSN(R⁴)₂, -N(R⁴)COR⁴, -N(R⁴)CSR⁴, -SO₂N(R⁴)₂, -N(R⁴)SO₂R⁴, -N(R⁴)CON(R⁴)₂, -N(R⁴)CSN(R⁴) and -N(R⁴)SO₂N(R⁴)₂ groups. In these substituents the group R⁴ when present is a hydrogen
 30 atom or a straight or branched alkyl group as defined above. Where more than one R⁴ group is present in a substituent each group may be the same or different. The substituent may be present on any available carbon atom or where appropriate any nitrogen atom, in the R¹ group.

35 In the compounds of formulae (1) and (1a), optionally substituted aromatic groups represented by the group R¹ include for example monocyclic or

bicyclic fused ring C₆₋₁₂ aromatic groups, such as phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups, optionally substituted by one, two, three or more L²(CH₂)_pL³(R^c)_q atoms or groups, where L², L³, p and q are as previously defined and R^c is as previously defined but is other than a hydrogen atom when L² and L³ is each a covalent bond and p is zero.

Optionally substituted heteroaromatic groups, represented by the group R¹ in compounds of formulae (1) and (1a) include for example optionally substituted C₁₋₉ heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Particular examples of heteroaromatic groups of these types include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-C₁₋₆aimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]-benzofuryl, benzothienyl, benzotriazolyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-dihydro]benzopyranyl, quinazoliny, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on R¹ heteroaromatic groups include one, two, three or more -L²(CH₂)_pL³(R^c)_q atoms or groups as just defined.

- 5 Examples of the substituents represented by R^a and R^b in compounds of formula (1) and which may be present on aromatic or heteroaromatic groups represented by R¹ include atoms or groups -L²(CH₂)_pLR^c, -L²(CH₂)_pR^c, -L²R^c, -(CH₂)_pR^c and -R^c wherein L², (CH₂)_p, L and R^c are as defined above. Particular examples of such substituents include
- 10 -L²CH₂L²R^c, -L²CH(CH₃)L³R^c, -L²(CH₂)₂L³R^c, -L²CH₂R^c, -L²CH(CH₃)R^c, -L²(CH₂)₂R^c, -CH₂R^c, -CH(CH₃)R^c and -(CH₂)₂R^c groups.

- Thus each of R^a and R^b and, where present, substituents on R¹ and aromatic or heteroaromatic groups in compounds of the invention may be
- 15 for example selected from a hydrogen atom, a halogen atom, e.g. a fluorine, chlorine, bromine or iodine atom, or a C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl, hydroxyethyl or -C(OH)(CF₃)₂, carboxyC₁₋₆alkyl, e.g. carboxyethyl, C₁₋₆alkylthio e.g.
- 20 methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, haloC₁₋₆alkyl, e.g. -CF₃, -CHF₂, CH₂F, haloC₁₋₆alkoxy, e.g. -OCF₃, -OCHF₂, -OCH₂F, C₁₋₆alkyl-
- 25 amino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkyl-
- 30 aminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy, e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkyl-
- 35 aminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, isopropylaminoethoxy, or dimethylaminopropoxy, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂R¹², C₁₋₆alkanoyl e.g. acetyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylamino-
- 35 sulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl, e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl,

- carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylamino-carbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylamino-carbonyl, e.g. aminoethylaminocarbonyl, C₁₋₆dialkylaminoC₁₋₆alkylamino-carbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋₆alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylaminocarbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylaminocarbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocabonyl-amino, C₁₋₆alkylaminothiocarbonylamino, e.g. methylaminothiocarbonyl-amino or ethylaminothiocarbonylamino, C₁₋₆dialkylaminothiocarbonyl-amino, e.g. dimethylaminothiocarbonylamino or diethylaminothiocarbonyl-amino, C₁₋₆alkylaminothiocarbonylC₁₋₆alkylamino, e.g. ethylaminothiocarbonylmethylamino, C₁₋₆alkylsulphonylamino, e.g. methylsulphonyl-amino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino, e.g. dimethylsulphonyl-amino or diethylsulphonylamino, aminosulphonylamino (-NHSO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonylamino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonyl-amino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, C₁₋₆alkanoylamino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoylamino, e.g. dimethyl-aminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino group.

Aromatic groups represented by the group Ar in compounds of formulae (1) and (1a) include optionally substituted monocyclic or bicyclic fused ring C₁₋₆ aromatic groups. Particular examples include optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl groups.

Optional substituents present on the aromatic groups represented by Ar include one, two, three or more substituents, each selected from an atom or group R⁶ in which R⁶ is -R^{6a} or -Alk³(R^{6a})_m, where R^{6a} is a halogen atom, or an amino (-NH₂), substituted amino, nitro, cyano, amidino,

hydroxyl (-OH), substituted hydroxyl, formyl, carboxyl (-CO₂H), esterified carboxyl, thiol (-SH), substituted thiol, -COR⁷ [where R⁷ is an -Alk³(R^{6a})_m, aryl or heteroaryl group], -CSR⁷, -SO₃H, -SO₂R⁷, -SO₂NH₂, -SO₂NHR⁷, SO₂N(R⁷)₂, -CONH₂, -CSNH₂, -CONHR⁷, -CSNHR⁷,
 5 -CON[R⁷]₂, -CSN(R⁷)₂, -N(R⁴)SO₂R⁷, -N(SO₂R⁷)₂, -NH(R⁴)SO₂NH₂, -N(R⁴)SO₂NHR⁷, -N(R⁴)SO₂N(R⁷)₂, -N(R⁴)COR⁷, -N(R⁴)CON(R⁷)₂, -N(R⁴)CSN(R⁷)₂, -N(R⁴)CSR⁷, -N(R⁴)C(O)OR⁷, -SO₂NHet¹ [where -NHet¹ is an optionally substituted C₅₋₇cyclicamino group optionally containing one or more other -O- or -S- atoms or -N(R⁴)-, -C(O)- or -C(S)- groups],
 10 -CONHet¹, -CSNHet¹, -N(R⁴)SO₂NHet¹, -N(R⁴)CONHet¹, -N(R⁴)CSNHet¹, -SO₂N(R⁴)Het² [where Het² is an optionally substituted monocyclic C₅₋₇carbocyclic group optionally containing one or more -O- or -S- atoms or -N(R⁴)-, -C(O)- or -C(S)- groups], -CON(R⁴)Het², -CSN(R⁴)Het², -N(R⁴)CON(R⁴)Het², -N(R⁴)CSN(R⁴)Het², aryl or heteroaryl
 15 group; Alk³ is a straight or branched C₁₋₆alkylene, C₂₋₆alkenylene or C₂₋₆alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or -S(O)_n [where n is an integer 1 or 2] or -N(R⁸)- groups [where R⁸ is a hydrogen atom or C₁₋₆alkyl, e.g. methyl or ethyl group]; and m is zero or an integer 1, 2 or 3. It will be appreciated that when two R⁴ or R⁷ groups
 20 are present in one of the above substituents, the R⁴ or R⁷ groups may be the same or different.

When in the group -Alk³(R^{6a})_m m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{6a} may be present on any
 25 suitable carbon atom in -Alk³. Where more than one R^{6a} substituent is present these may be the same or different and may be present on the same or different atom in -Alk³. Clearly, when m is zero and no substituent R^{6a} is present the alkylene, alkenylene or alkynylene chain represented by Alk³ becomes an alkyl, alkenyl or alkynyl group.

30 When R^{6a} is a substituted amino group it may be for example a group -NHR⁷ [where R⁷ is as defined above] or a group -N(R⁷)₂ wherein each R⁷ group is the same or different.

35 When R^{6a} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

When R^{6a} is a substituted hydroxyl or substituted thiol group it may be for example a group $-OR^7$ or a $-SR^7$ or $-SC(=NH)NH_2$ group respectively.

- 5 Esterified carboxyl groups represented by the group R^{6a} include groups of formula $-CO_2Alk^4$ wherein Alk^4 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a C_{6-12} aryl C_{1-8} alkyl group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a C_{6-12} aryl group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a C_{6-12} aryloxy C_{1-8} alkyl group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyl-oxymethyl, or 2-naphthyl-oxymethyl group; an optionally substituted C_{1-8} alkanoyloxy C_{1-8} alkyl group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a C_{6-12} aroyloxy C_{1-8} alkyl group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^4 group include R^{6a} substituents described above.
- 15
- 20 When Alk^3 is present in or as a substituent it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three $-O-$ or $-S-$, atoms or
- 25 $-S(O)-$, $-S(O)_2-$ or $-N(R^8)-$ groups.

Aryl or heteroaryl groups represented by the groups R^{6a} or R^7 include mono- or bicyclic optionally substituted C_{6-12} aromatic or C_{1-9} heteroaromatic groups as described above for the groups R^1 and Het.

- 30 The aromatic and heteroaromatic groups may be attached to the remainder of the compound of formula (1) by any carbon or hetero e.g. nitrogen atom as appropriate.

- 35 When $-NHet^1$ or $-Het^2$ forms part of a substituent R^6 each may be for example an optionally substituted pyrrolidinyl, pyrazolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, piperidinyl or thiazolidinyl group. Additionally

Het² may represent for example, an optionally substituted cyclopentyl or cyclohexyl group. Optional substituents which may be present on -NHet¹ or -Het² include those R⁵ substituents described above.

- 5 Particularly useful atoms or groups represented by R⁶ include fluorine, chlorine, bromine or iodine atoms, or C₁₋₆alkyl, e.g. methyl, ethyl, n-propyl, i-propyl, n-butyl or t-butyl, optionally substituted phenyl, pyridyl, pyrrolyl, furyl, thiazolyl, or thienyl, C₁₋₆alkylamino, e.g. methylamino or ethylamino, C₁₋₆hydroxyalkyl, e.g. hydroxymethyl or hydroxyethyl, carboxyC₁₋₆alkyl,
- 10 e.g. carboxyethyl, C₁₋₆alkylthio e.g. methylthio or ethylthio, carboxyC₁₋₆alkylthio, e.g. carboxymethylthio, 2-carboxyethylthio or 3-carboxypropylthio, C₁₋₆alkoxy, e.g. methoxy or ethoxy, hydroxyC₁₋₆alkoxy, e.g. 2-hydroxyethoxy, optionally substituted phenoxy, pyridyloxy, thiazolyoxy, phenylthio or pyridylthio, C₅₋₇cycloalkoxy, e.g. cyclopentyloxy, haloC₁₋
- 15 6alkyl, e.g. trifluoromethyl, haloC₁₋₆alkoxy, e.g. trifluoromethoxy, C₁₋₆alkylamino, e.g. methylamino or ethylamino, amino (-NH₂), aminoC₁₋₆alkyl, e.g. aminomethyl or aminoethyl, C₁₋₆dialkylamino, e.g. dimethylamino or diethylamino, C₁₋₆alkylaminoC₁₋₆alkyl, e.g. ethylaminoethyl, C₁₋₆dialkylaminoC₁₋₆alkyl, e.g. diethylaminoethyl, aminoC₁₋₆alkoxy,
- 20 e.g. aminoethoxy, C₁₋₆alkylaminoC₁₋₆alkoxy, e.g. methylaminoethoxy, C₁₋₆dialkylaminoC₁₋₆alkoxy, e.g. dimethylaminoethoxy, diethylaminoethoxy, isopropylaminoethoxy, or dimethylaminopropoxy, imido, such as phthalimido or naphthalimido, e.g. 1,8-naphthalimido, nitro, cyano, amidino, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO₂H), -CO₂Alk⁴ [where Alk⁴
- 25 is as defined above], C₁₋₆alkanoyl e.g. acetyl, optionally substituted benzoyl, thiol (-SH), thioC₁₋₆alkyl, e.g. thiomethyl or thioethyl, -SC(=NH)NH₂, sulphonyl (-SO₃H), C₁₋₆alkylsulphonyl, e.g. methylsulphonyl, aminosulphonyl (-SO₂NH₂), C₁₋₆alkylaminosulphonyl, e.g. methylaminosulphonyl or ethylaminosulphonyl, C₁₋₆dialkylaminosulphonyl,
- 30 e.g. dimethylaminosulphonyl or diethylaminosulphonyl, phenylaminosulphonyl, carboxamido (-CONH₂), C₁₋₆alkylaminocarbonyl, e.g. methylaminocarbonyl or ethylaminocarbonyl, C₁₋₆dialkylaminocarbonyl, e.g. dimethylaminocarbonyl or diethylaminocarbonyl, aminoC₁₋₆alkylaminocarbonyl, e.g. aminoethylaminocarbonyl, C₁₋₆dialkylaminoC₁₋₆alkylaminocarbonyl, e.g. diethylaminoethylaminocarbonyl, aminocarbonylamino, C₁₋
- 35 6alkylaminocarbonylamino, e.g. methylaminocarbonylamino or ethylamino-

carbonylamino, C₁₋₆dialkylaminocarbonylamino, e.g. dimethylamino-carbonylamino or diethylaminocarbonylamino, C₁₋₆alkylaminocarbonylC₁₋₆alkylamino, e.g. methylaminocarbonylmethylamino, aminothiocabonyl-amino, C₁₋₆alkylaminothiocabonylamino, e.g. methylaminothiocabonyl-
 5 amino or ethylaminothiocabonylamino, C₁₋₆dialkylaminothiocabonyl-amino, e.g. dimethylaminothiocabonylamino or diethylaminothiocabonyl-amino, C₁₋₆alkylaminothiocabonylC₁₋₆alkylamino, e.g. ethylaminothiocabonylmethylamino, -CONHC(=NH)NH₂, C₁₋₆alkylsulphonylamino, e.g. methylsulphonylamino or ethylsulphonylamino, C₁₋₆dialkylsulphonylamino,
 10 e.g. dimethylsulphonylamino or diethylsulphonylamino, optionally substituted phenylsulphonylamino, aminosulphonylamino (-NH₂SO₂NH₂), C₁₋₆alkylaminosulphonylamino, e.g. methylaminosulphonyl-amino or ethylaminosulphonylamino, C₁₋₆dialkylaminosulphonylamino, e.g. dimethylaminosulphonylamino or diethylaminosulphonylamino, optionally
 15 substituted morpholinesulphonylamino or morpholinesulphonylC₁₋₆alkyl-amino, optionally substituted phenylaminosulphonylamino, C₁₋₆alkanoyl-amino, e.g. acetylamino, aminoC₁₋₆alkanoylamino e.g. aminoacetylamino, C₁₋₆dialkylaminoC₁₋₆alkanoyl-amino, e.g. dimethylaminoacetylamino, C₁₋₆alkanoylaminoC₁₋₆alkyl, e.g. acetylaminomethyl, C₁₋₆alkanoylaminoC₁₋₆alkylamino, e.g. acetamidoethylamino, C₁₋₆alkoxycarbonylamino, e.g. methoxycarbonylamino, ethoxycarbonylamino or t-butoxycarbonylamino or
 20 optionally substituted benzyloxy, pyridylmethoxy, thiazolylmethoxy, benzyloxycarbonylamino, benzyloxycarbonylaminoC₁₋₆alkyl e.g. benzyloxycarbonylaminoethyl benzothio, pyridylmethylthio or thiazolylmethylthio
 25 groups.

Where desired, two R⁶ substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C₁₋₆alkylenedioxy group such as methylenedioxy or ethylenedioxy.

30

It will be appreciated that where two or more R⁶ substituents are present, these need not necessarily be the same atoms and/or groups. In general, the substituent(s) may be present at any available ring position in the heteroaromatic group represented by Het.

35

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and
5 organic bases:

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isothionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or
10 napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts
15 such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include
20 pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

R in compounds of the invention is preferably a $-CO_2H$ group.

25 When present, the aliphatic chain represented by Alk^1 in compounds of the invention is preferably a $-CH_2-$ chain.

Alk^2 in compounds of formula (1) is preferably a $-CH_2-$ chain and m is preferably an integer 1. In compounds of this type, the carbon atom to
30 which Alk^2 and R are attached forms a chiral centre and is preferably in the L configuration.

R^2 in compounds of formula (1) is preferably a hydrogen atom.

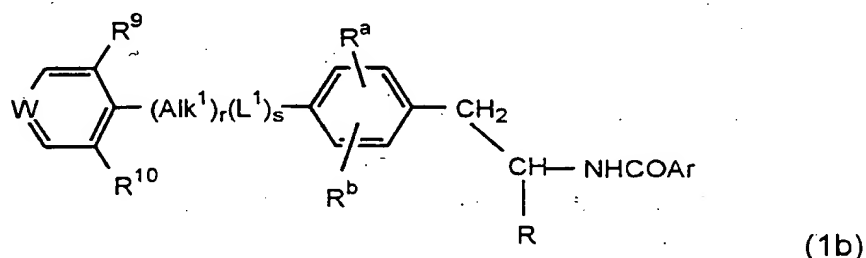
35 R^3 in compounds of the invention is preferably a hydrogen atom.

In general in compounds of the invention $-(\text{Alk}^1)_n(\text{L}^1)_s-$ is preferably $-\text{CH}_2\text{O}-$, $-\text{SO}_2\text{NH}-$, $-\text{C}(\text{O})\text{O}-$ or $-\text{CON}(\text{R}^4)-$ and is especially $-\text{CONH}-$.

5 In general in compounds of the invention the group R^1 is preferably an optionally substituted aromatic or heteroaromatic group. Particularly useful groups of these types include optionally substituted phenyl, pyridyl or pyrimidinyl groups, particularly those in which the substituent when present is an atom or group $-\text{L}^2(\text{CH}_2)_p\text{L}^3(\text{R}^c)_q$ as described above. Each substituent may be present on any available ring carbon or nitrogen atom.

10 The aromatic group represented by Ar in compounds of formulae (1) and (1a) is preferably an optionally substituted phenyl group. Each optional substituent when present is preferably an atom or group R^6 as defined above.

15 A particularly useful class of compounds according to the invention has the formula (1b)



20 wherein $-\text{W}=$ is $-\text{CH}=$ or $-\text{N}=$, R^9 and R^{10} , which may be the same or different, is each a $-\text{L}^2(\text{CH}_2)_p\text{L}^3(\text{R}^c)_q$ atom or group as generally and particularly defined above, and Alk^1 , r , L^1 , s , R^a , R^b , R and Ar are as generally and particularly defined above, and the salts, solvates, hydrates
25 and N-oxides thereof.

It will be appreciated that the various preferences stated above in relation to groups present in compounds of formulae (1) and (1a) apply equally to the same groups when present in compounds of formula (1b).

30

Additionally, in compounds of formula (1b) $-(\text{Alk}^1)_r(\text{L}^1)_r-$ is preferably a $-\text{CH}_2\text{O}$ or $-\text{CON}(\text{R}^4)-$ group and is especially a $-\text{CONH}-$ group.

Ar is preferably an optionally substituted phenyl group. Particularly useful
5 compounds of formula (1b) are those wherein Ar is a 2-, 3- or 4-monosubstituted or a 2,6-disubstituted phenyl group.

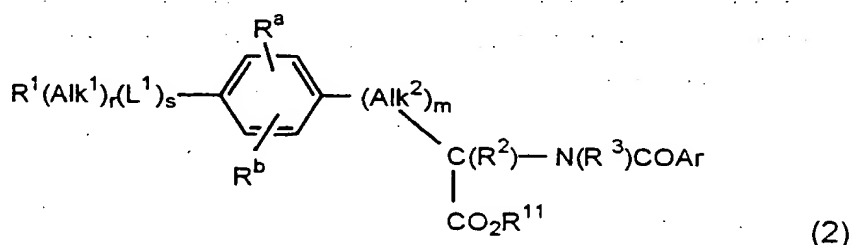
One of R^9 or R^{10} in compounds of formula (1a) may be for example a hydrogen atom and the other a substituent $\text{L}^2(\text{CH}_2)_p\text{L}^3(\text{R}^c)_q$ in which R^c is
10 not a covalent bond and p is zero, but preferably each of R^9 and R^{10} is a substituent $-\text{L}^2(\text{CH}_2)_p\text{L}^3(\text{R}^c)_q$ where R^c is as just defined. Particularly useful R^9 or R^{10} substituents include a hydrogen atom or halogen atom, especially fluorine or chlorine atoms, or a methyl, ethyl, methoxy, ethoxy,
-CF₃, -OH, -CN, -NO₂, -NH₂, -NHCH₃, -N(CH₃)₂, -COCH₃, -SCH₃, -CO₂H
15 or -CO₂CH₃ group.

Particularly useful compounds according to the invention include the following:

- (N-2,6-Dimethoxybenzoyl)-[O-(3,5-dichloro-4-pyridinyl)methyl]-L-tyrosine;
20 2-Carboxybenzoyl-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
(N-2,6-Dimethoxybenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
(N-3-Carboxybenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
25 (N-4-Carboxybenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
(N-2-t-Butoxycarbonylbenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
(N-3-Cyanobenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
30 [N-3-(1-H-Tetrazol-5-yl)]-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
[N-(3-Methoxycarbonylbenzoyl)]-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
35 and the salts, solvates, hydrates and N-oxides thereof.

The compounds of formulae (1), (1a) and (1b) may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols R^1 - R^3 , L^1 , Alk^1 , R^a , R^b , Alk^2 , m , r , s and Ar when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of the desired compound and the processes described hereinafter are to be understood to extend to such removal of protecting groups. For convenience, the processes described below all refer to the preparation of a compound of formula (1) but clearly the description applies equally to the preparation of compounds of formulae (1a) and (1b).

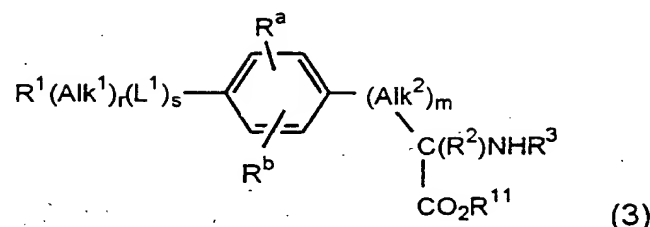
Thus a compound of formula (1) may be obtained by hydrolysis of an ester of formula (2):



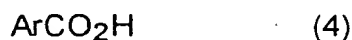
where R^{11} is an alkyl group.

The hydrolysis may be performed using either an acid or a base depending on the nature of R^9 , for example an organic acid such as trifluoroacetic acid or an inorganic base such as lithium hydroxide optionally in an aqueous organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran or dioxane or an alcohol, e.g. methanol at around ambient temperature. Where desired, mixtures of such solvents may be used.

Esters of formula (2) may be prepared by coupling an amine of formula (3):



(where R^{11} is as just described) or a salt thereof with an acid of formula (4):



or an active derivative thereof.

Active derivatives of acids of formula (4) include anhydrides, esters and halides. Particular esters include pentafluorophenyl or succinyl esters.

The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, an ether, e.g. a cyclic ether such as tetrahydrofuran, or a halogenated hydrocarbon, such as dichloromethane, at a low temperature, e.g. around -30°C to around ambient temperature, optionally in the presence of a base, e.g. an organic base such as an amine, e.g. triethylamine, pyridine, or dimethylaminopyridine, or a cyclic amine, such as N-methylmorpholine.

Where an acid of formula (4) is used, the reaction may additionally be performed in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or N,N'-dicyclohexylcarbodiimide, advantageously in the presence of a catalyst such as a N-hydroxy compound e.g. a N-hydroxytriazole such as 1-hydroxybenzotriazole. Alternatively, the acid may be reacted with a chloroformate,

for example ethylchloroformate, prior to reaction with the amine of formula (3).

Intermediates of formulae (2), (3) and (4), or compounds of formula (1),
5 may be manipulated to introduce substituents to aromatic or heteroaromatic groups or modify existing substituents in groups of these types. Typically, such manipulation may involve standard substitution approaches employing for example alkylation, arylation, heteroarylation, acylation, thioacylation, halogenation, sulphonylation, nitration, formylation
10 or coupling reactions. Alternatively, existing substituents may be modified for example by oxidation, reduction or cleavage reactions. Particular examples of such reactions are given below. Where these are particularly described in relation to the generation of the group $R^1(Alk^1)_r(L^1)_s$, it will be appreciated that each reaction may also be used to introduce or modify
15 R^5 and/or R^6 substituents in for example Ar groups as appropriate.

Thus in one example, a compound wherein $R^1(Alk^1)_r(L^1)_s$ is a $-L^1H$ group may be alkylated, arylated or heteroarylated using a reagent $R^1(Alk^1)_rX$ in which R^1 is other than a hydrogen atom and X is a leaving atom or group
20 such as a halogen atom, e.g. a fluorine, bromine, iodine or chlorine atom or a sulphonyloxy group such as an alkylsulphonyloxy, e.g. trifluoromethylsulphonyloxy or arylsulphonyloxy, e.g. p-toluenesulphonyloxy group.

The reaction may be carried out in the presence of a base such as a
25 carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran.

30 In another example, a compound where $R^1(Alk^1)_r(L^1)_s$ is a $-L^1H$ group is a hydrogen atom may be functionalised by acylation or thioacylation, for example by reaction with a reagent $R^1(Alk^1)_rL^1X$ [wherein L^1 is a $-C(O)-$, $C(S)-$, $-N(R^4)C(O)-$ or $N(R^4)C(S)-$ group], in the presence of a base, such as a hydride, e.g. sodium hydride or an amine, e.g. triethylamine or N-methylmorpholine, in a solvent such as a halogenated hydrocarbon, e.g.
35

dichloromethane or carbon tetrachloride or an amide, e.g. dimethylformamide, at for example ambient temperature, or by reaction with $R^1(Alk^1)_rCO_2H$, $R^1(Alk^1)_4COSH$ or an activated derivative thereof, for example as described above for the preparation of esters of formula (2).

5

In a further example a compound may be obtained by sulphonylation of a compound where $R^1(Alk^1)_r(L^1)_s$ is an -OH group by reaction with a reagent $R^1(Alk^1)_rL^1Hal$ [in which L^1 is -S(O)- or -SO₂- and Hal is a halogen atom such as chlorine atom] in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature.

10

In another example, a compound where $R^1(Alk^1)_r(L^1)_s$ is a -L¹H group, may be coupled with a reagent R^1OH (where R^1 is other than a hydrogen atom) or R^1Alk^1OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl, diisopropyl- or dimethylazodicarboxylate to yield a compound containing a $R^1(Alk^1)_rO$ - group.

15

20

In a further example, ester groups -CO₂R⁴ or -CO₂Alk⁴ in compounds of formula (1) may be converted to the corresponding acid [-CO₂H] by acid- or base-catalysed hydrolysis depending on the nature of the group R⁴ or Alk⁴. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxane or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol.

25

In a second example, -OR⁷ [where R⁷ represents an alkyl group such as methyl group] groups in compounds of formula (1) may be cleaved to the corresponding alcohol -OH by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

30
35

Alcohol [-OH] groups may also be obtained by hydrogenation of a corresponding -OCH₂R⁷ group (where R⁷ is an aryl group) using a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate, cyclohexadiene or hydrogen, from around ambient to the reflux temperature. In another example, -OH groups may be generated from the corresponding ester [-CO₂Alk⁴ or CO₂R⁴] or aldehyde [-CHO] by reduction, using for example a complex metal hydride such as lithium aluminium hydride or sodium borohydride in a solvent such as methanol.

In another example, alcohol -OH groups in compounds of formula (1) may be converted to a corresponding -OR³ group by coupling with a reagent R⁷OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

Aminosulphonylamino [-NHSO₂NH₂] groups in compounds of formula (1) may be obtained, in another example, by reaction of a corresponding amine [-NH₂] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In a further example amine (-NH₂) groups may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohydride or sodium cyanoborohydride, in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane, a ketone such as acetone, or an alcohol, e.g. ethanol, where necessary in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amine [-NH₂] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO₂] group may be reduced to an amine [-NH₂], for example by catalytic hydrogenation using for example hydrogen

in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol e.g. methanol, or by chemical reduction using for example a metal, e.g. tin or iron, in the presence of an acid such as hydrochloric acid.

5

Aromatic halogen substituents in compounds of the invention may be subjected to halogen-metal exchange with a base, for example a lithium base such as n-butyl or t-butyl lithium, optionally at a low temperature, e.g. around -78°C, in a solvent such as tetrahydrofuran and then quenched with an electrophile to introduce a desired substituent. Thus, for example, a formyl group may be introduced by using dimethylformamide as the electrophile; a thiomethyl group may be introduced by using dimethyldisulphide as the electrophile.

15 In another example, sulphur atoms in compounds of the invention, for example when present in the linker group L¹ may be oxidised to the corresponding sulfoxide using an oxidising agent such as a peroxy acid, e.g. 3-chloroperoxybenzoic acid, in an inert solvent such as a halogenated hydrocarbon, e.g. dichloromethane, at around ambient temperature.

20

Intermediates of formulae (3) and (4), R¹(Alk¹)_rX, R¹(Alk¹)_rL¹X, R¹(Alk¹)_rCO₂H, R¹OH and R¹Alk¹OH for use in the above processes are either known compounds or may be prepared from known starting materials by use of analogous processes to those used for the preparation of the known compounds and/or by treating known compounds by one or more of the alkylation, acylation and other manipulations described herein, such as particularly described for the preparation of the Intermediates in the exemplification section hereinafter.

25
30 N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid in a solvent, e.g. dichloromethane, at ambient temperature.

35

Salts of compounds of formula (1) may be prepared by reaction of a compound of formula (1) with an appropriate base in a suitable solvent or mixture of solvents e.g. an organic solvent such as an ether e.g. diethylether, or an alcohol, e.g. ethanol using conventional procedures.

5

Where it is desired to obtain a particular enantiomer of a compound of formula (1) this may be produced from a corresponding mixture of enantiomers using any suitable conventional procedure for resolving enantiomers.

10

Thus for example diastereomeric derivatives, e.g. salts, may be produced by reaction of a mixture of enantiomers of formula (1) e.g. a racemate, and an appropriate chiral compound, e.g. a chiral base. The diastereomers may then be separated by any convenient means, for example by crystallisation and the desired enantiomer recovered, e.g. by treatment with an acid in the instance where the diastereomer is a salt.

15

In another resolution process a racemate of formula (1) may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described above.

20

The following Examples illustrate the invention. All temperatures are in °C. The following abbreviations are used:

- | | | |
|----|---|------------------------------------|
| 25 | EDC - 1-(3-dimethylaminopropyl)3-ethylcarbodiimide; | |
| | DMF - dimethylformamide; | DMSO - dimethylsulphoxide; |
| | HOBT - 1-hydroxybenzotriazole; | THF - tetrahydrofuran; |
| | NMM - N-methylmorpholine; | DCM - dichloromethane; |
| | Ph - phenyl; | Boc - <u>tert</u> -butoxycarbonyl; |
| 30 | EtOAc - ethyl acetate; | MeOH - methanol; |
| | Ar - aryl; | Me - methyl; |
| | Et ₂ O - diethylether; | EtOH - ethanol; |

INTERMEDIATE 1

35 **N-(2,6-Dimethoxybenzoyl)-(O-benzyl)-L-tyrosine methyl ester**

EDC (212mg, 1.1mmol) was added to a solution of (Q-benzyl)tyrosine methyl ester hydrochloride (322mg, 1mmol), 2,6-dimethoxybenzoic acid (182mg, 1mmol), HOBT (149mg, 1.1mmol) and NMM (242μl, 2.2mmol) in DCM (10ml). The mixture was stirred at room temperature overnight, then
 5 diluted with DCM (100ml), washed with 10% citric acid (20ml), saturated sodium bicarbonate solution (20ml) and brine (20ml), dried (Na₂SO₄) and evaporated under reduced pressure. The residue was purified by column chromatography (SiO₂; EtOAc/hexane, 60:40) to give the title compound as a colourless gum (392mg, 87%). δH (CDCl₃) 7.44-7.31 (5H, m, OCH₂Ph), 7.29 (1H, t, J 8.4Hz, Ar(OMe)H), 7.14 (2H, d, J 8.7Hz, CH₂Ar(O)H), 6.88 (2H, d, J 8.7Hz, CH₂Ar(O)H), 6.55 (2H, d, J 8.4Hz, Ar(OMe)H), 6.36 (1H, br d, J 7.4Hz, CONH), 5.11 (1H, dt, J 7.5, 5.2Hz, CH_αtyr) 5.02 (2H, s, OCH₂Ph), 3.80 (6H, s, 2 x ArOMe), 3.72 (3H, s, CO₂Me), 3.29 (1H, dd, J 5.5, 14.0Hz, CHCH_AH_BAr) and 3.16 (1H, dd, J
 10 4.9, 14.0Hz, CHCH_AH_BAr); m/z (ESI, 15V) 450 (Mh⁺).

INTERMEDIATE 2

2-Thio(S-4-methylphenyl)benzoyl-(O-2,6-dichlorobenzyl)-L-tyrosine methyl ester

A solution of (Q-2,6-dichlorobenzyl)-L-tyrosine methyl ester hydrochloride (0.39g, 1mmol), 2-thio(S-4-methylphenyl)benzoic acid (0.24g, 1mmol), EDC (0.21g, 1.1mmol), HOBT (0.16g, 1.2mmol) and NMM (0.28ml; 0.25g, 2.5mmol) in DMF (5ml) was stirred at room temperature for 16h. The solvent was evaporated *in vacuo* and the residue partitioned between 10%
 25 hydrochloric acid (10ml) and DCM (20ml). The aqueous layer was extracted with DCM (20ml) and the combined organic layers washed with NaHCO₃ solution (25ml), dried over MgSO₄ and the solvent removed to give a brown oil that was purified by column chromatography (SiO₂; 2:5 EtOAc/hexane) to give an off-white solid that was recrystallised from
 30 EtOAc/hexane (1:2) to give the title compound as a white solid (0.24g, 41%). δH (CDCl₃) 7.53-6.90 (15H, m), 6.81 (1H, d, J 7.3Hz), 5.22 (2H, s), 5.05 (1H, m), 3.77 (3H, s), 3.27 (1H, dd, J 5.9, 14.0Hz), 3.18 (1H, dd, J 5.2, 14.0Hz) and 2.35 (3H, s).

INTERMEDIATE 3

Methyl phthalate

Solid sodium methoxide (5.4g, 0.1mmol) was added to a suspension of phthalic anhydride (14.8g, 0.1mmol) in MeOH (100ml) and the reaction mixture stirred for 2h at room temperature. The solvent was evaporated *in vacuo*, and the residue partitioned between DCM and 1.0M hydrochloric acid. The aqueous layer was extracted with DCM (2 x 20ml), and the combined organic layers dried over MgSO₄. The solvent was removed to give the title compound as a white solid (17.3g, 96%). δ H (CDCl₃) 7.94-7.91 (1H, m), 7.70-7.63 (1H, m), 7.61-7.54 (2H, m) and 3.92 (3H, s).

10 INTERMEDIATE 4

a) 2-(Methoxycarbonyl)benzoyl-(N-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester

Intermediate 3 (0.681g, 3.78mmol) was dissolved in dry DMF (20ml) and (N-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester hydrochloride (4mmol; prepared from 3,5-dichloro-4-picoloyl chloride and N-Boc-L-4-aminophenylalanine methyl ester) added in one portion. To the mixture was added NMM (0.896ml, 8.16mmol), HOBT.H₂O (0.551g, 4.08mmol) and EDC (0.783g, 4.08mmol). The reaction mixture was stirred under argon at room temperature for 2.5h, poured into 50% saturated sodium bicarbonate solution (100ml) and extracted with EtOAc (2 x 50ml). The organic layer was washed with 50% saturated sodium bicarbonate solution (1 x 50ml), 10% citric acid (1 x 50ml), brine (1 x 50ml), and dried over MgSO₄. The solvent was evaporated to give a white foam which was purified by chromatography (SiO₂; gradient elution DCM to DCM/MeOH (99:1)) to give the title compound as a white foam (1.0g, 51%). δ H (DMSO-d₆) 10.86 (1H, s), 8.92 (1H, d, \downarrow 7.9Hz), 8.79 (2H, s), 7.70 (1H, dd, \downarrow 7.29, 1.3Hz), 7.63-7.52 (4H, m), 7.37 (1H, dd, \downarrow 7.5, 1.3Hz), 7.30 (2H, d, \downarrow 8.0Hz), 4.66-4.58 (1H, m), 3.67 (3H, s), 3.363 (3H, s) and 3.15-2.95 (2H, m).

30

The following compound was prepared in a similar manner using 3-cyanobenzoic acid in place of Intermediate 3:

35 b) (N-3-Cyanobenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester

δ H (CDCl₃) 8.55 (2H, s), 8.1-7.5 (7H, m), 7.12 (2H, d, \downarrow 8.5Hz), 6.7 (1H, d, \downarrow 8.5Hz), 5.15-5.05 (1H, m), 3.82 (3H, s) and 3.35-3.18 (2H, m). m/z (ES) 497 (MH⁺).

- 5 Using a similar procedure to Intermediate 4a) employing the phenylalanine t-butyl ester in place of the corresponding methyl ester, the following compound was prepared:

c) [N-3-(Methoxycarbonyl)benzoyl]-(N'-3,5-dichloroisonicotinoyl)-
10 L-4-aminophenylalanine t-butyl ester
 δ H (CDCl₃) 8.44 (2H, s), 7.92-7.2 (9H, m), 6.53 (1H, d, \downarrow 7.8Hz), 4.99-4.93 (1H, m), 3.85 (3H, s), 3.23 (2H, d, \downarrow 5.6Hz) and 1.46 (9H, s). m/z (ES) 572 (MH⁺).

15 INTERMEDIATE 5

Benzyl-4-{2-[(diphenylmethylene)amino]-3-ethoxy-3-oxopropyl}benzoate

A mixture of benzyl-4-(bromomethyl)benzoate (7.61g, 24.9mmol), N-(diphenylmethylene)glycine ethyl ester (6.66g, 24.9mmol) and potassium carbonate (6.9g, 50mmol) in acetonitrile (300ml) were heated to reflux for
20 20h. The reaction was concentrated *in vacuo*, and the residue partitioned between EtOAc (100ml) and water (100ml). The aqueous layer was extracted with EtOAc (100ml) and the combined organic layers were dried (Na₂SO₄), and concentrated *in vacuo* to give the title compound as a pale
25 straw coloured oil (13.0g) which was used without further purification. δ H (CDCl₃) 7.90 (2H, d, \downarrow 8.3Hz, Ar-H), 7.58 (2H, d, \downarrow 7.3Hz, Ar-H), 7.50-7.25 (13H, m, Ar-H), 7.14 (2H, d, \downarrow 8.1Hz, Ar-H), 6.65 (2H, d, \downarrow 6.8Hz, CH₂Ph), 5.33 (2H, m, CHCH₂Ar), 4.30-4.15 (3H, m, CHCH₂Ar) and CH₂CH₃) and 1.26 (3H, t, \downarrow 7.1Hz, CH₂CH₃). m/z (ESI, 60V) 492 (MH⁺).

30

INTERMEDIATE 6

4-(Benzyloxycarbonyl)phenylalanine ethyl ester hydrochloride

A solution of Intermediate 5 (13.0g, 25mmol) in THF (200ml) was treated with hydrochloric acid (2.0M solution, 20ml, 40mmol) and stirred at room
35 temperature for 2h. then concentrated *in vacuo* and triturated with Et₂O to give a white solid which was purified by recrystallisation from EtOH/EtOAc

to give the title compound as a white solid (4.24g, 47%). δ H (DMSO- d_6) 7.96 (2H, dd, J 6.6, 1.7Hz, Ar-H), 7.48-7.37 (7H, 6m, Ar-H), 5.35 (2H, s, CH_2Ph), 4.29 (1H, dd, J 7.7, 5.0Hz, $CH\alpha$), 4.11 (2H, q, J 7.1Hz, CH_2CH_3), 3.27 (1H, dd, J 14.0, 5.9Hz, $CHCH_AH_BAr$), 3.15 (1H, dd, J 14.0, 7.7Hz, $CHCH_AH_BAr$) and 1.08 (3H, t, J 7.1Hz, CH_2CH_3), m/z (ESI, 60V) 328 (MH^+),

INTERMEDIATE 7

(N-2,6-Dimethoxybenzoyl)-4-(benzyloxycarbonyl)phenylalanine ethyl ester

A solution of Intermediate 6 (2.75g, 8.4mmol) and NMM (1.25mg, 11.2mmol) in DCM (50ml) was treated with 2,6-dimethoxybenzoyl chloride (2.25g, 11.2mmol) and stirred for 16h at room temperature. The solution was concentrated *in vacuo* and partitioned between dilute HCl (50ml) and EtOAc (100ml). The aqueous layer was extracted with EtOAc (2 x 50ml) and the combined organic layers washed with water (100ml) and $NaHCO_3$ solution (100ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a pale amber glass (3.36g, 82%) which was used without further purification. δ H ($CDCl_3$) 7.96 (2H, d, J 8.4Hz, Ar-H), 7.45-7.28 (8H, m, Ar-H), 6.56 (2H, d, J 8.4Hz, Ar-H), 6.37 (1H, d, J 7.2Hz, NH), 5.34 (2H, s, $COCH_2Ph$), 5.13 (1H, m, $CH\alpha$), 4.16 (2H, q, J 7.1Hz, CH_2CH_3), 3.80 (6H, s, OMe), 3.42 (1H, dd, J 13.8, 5.7Hz, $CHCH_AH_BAr$), 3.26 (1H, dd, J 13.8, 4.9Hz, $CHCH_AH_BAr$) and 1.25 (3H, t, J 7.1Hz, CH_2CH_3). m/z (ESI, 60V) 492 (MH^+).

INTERMEDIATE 8

(N-2,6-Dimethoxybenzoyl)-4-carboxyphenylalanine ethyl ester

A solution of Intermediate 7 (3.35g, 6.8mmol) in EtOH (300ml) was treated with 10% palladium on charcoal (400mg) and stirred under an atmosphere of H_2 for 20h. The catalyst was removed by filtration through Celite® and the solution concentrated *in vacuo* to give the title compound as a glass (2.78g, 100%). δ H ($CDCl_3$) 7.99 (2H, d, J 8.2Hz, Ar-H), 7.36 (2H, d, J 8.2Hz, Ar-H), 7.27 (1H, t, J 8.4Hz, Ar-H), 6.55 (2H, d, J 8.4Hz, Ar-H), 6.42 (1H, d, J 7.3Hz, NH), 5.15 (1H, m, $CH\alpha$), 4.18 (2H, q, J 7.1Hz, CH_2CH_3), 3.81 (6H, s, OMe), 3.45 (1H, dd, J 13.7, 5.6Hz, $CHCH_AH_BAr$), 3.28 (1H,

dd, \downarrow 13.7, 6.9Hz, $\text{CHCH}_A\text{H}_B\text{Ar}$) and 1.26 (3H, t, \downarrow 7.1Hz, CH_2CH_3). m/z (ESI, 60V) 402 (MH^+).

INTERMEDIATE 9

5 (N-2,6-Dimethoxybenzoyl)-4-(benzylaminocarbonyl)phenylalanine ethyl ester

A solution of Intermediate 8 (0.73g, 1.82mmol) in DCM (40ml) was treated with oxalyl chloride (5ml) and DMF (1 drop) and stirred at room temperature for 2h. The solvent was removed *in vacuo* and the residue
 10 azeotroped with toluene, dissolved in DCM (40ml), and treated with benzylamine (1.0ml) and stirred at room temperature for 3h. The reaction was concentrated *in vacuo* and partitioned between dilute HCl (1.0M, 30ml) and EtOAc (50ml). The aqueous layer was extracted with EtOAc (3 x 50ml) and the combined organic layers washed with NaHCO_3 solution (2
 15 x 50ml) and brine (50ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound as a white solid (1.07g) which was used without further purification. δH (CDCl_3) 7.75 (1H, br s, NH), 7.69 (2H, d, \downarrow 8.3Hz, ArH), 7.38-7.24 (8H, m, Ar-H), 6.65 (2H, d, \downarrow 8.4Hz, Ar-H), 6.36 (1H, d, \downarrow 6.9Hz, Ar-H), 5.12 (1H, m, CH_α), 4.63 (2H, d, \downarrow 5.6Hz, NHCH_2Ph), 4.16
 20 (2H, q, \downarrow 7.1Hz, CH_2CH_3), 3.80 (6H, s, OMe), 3.40 (1H, dd, \downarrow 13.8, 5.8Hz, $\text{CHCH}_A\text{H}_B\text{Ar}$), 3.25 (1H, dd, \downarrow 13.8, 4.9Hz, $\text{CHCH}_A\text{H}_B\text{Ar}$) and 1.25 (3H, t, \downarrow 7.1Hz, CH_2CH_3). m/z (ESI, 60V) 491 (MH^+).

INTERMEDIATE 10

25 [N-3-(1-H-Tetrazol-5-yl)benzyl]-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester

To Intermediate 4b) (0.424g, 0.85mmol) in dry toluene (10ml) was added trimethylsilyl azide (0.22ml) and di-n-butyl tin oxide (21mg). The solution was refluxed overnight, cooled and then evaporated. Chromatography on
 30 silica gel eluting with EtOAc hexane 50:50 afforded the title compound as a foam (0.214g, 46%). δH (CD_3OD), 8.6 (2H, s), 8.4-7.42 (6H, m), 7.3 (2H, d, \downarrow 8.5Hz), 4.92 (1H, m), 4.8 (3H, s) and 3.18-3.09 (2H, m). m/z (ES) 497 (MH^+).

35 INTERMEDIATE 11

3,5-Dichloro-4-hydroxymethylpyridine

A solution of 3,5-dichloropyridine-4-carboxaldehyde (1.34g, 7.6mmol) in MeOH (10ml) was treated with NaBH₄ (0.29g, 7.6mmol) and stirred at room temperature for 2h. The reaction was quenched with water (5ml) and concentrated *in vacuo*. The residue was partitioned between EtOAc (20ml) and 10% HCl (10ml). The aqueous layer was extracted with EtOAc and the combined organic extracts, washed with 10% NaHCO₃ solution, dried (MgSO₄) and concentrated *in vacuo* to give the title compound as a white solid (1.05g, 78%). δ H (CDCl₃) 8.52 (2H, s, pyr-H), 4.94 (2H, br s, CH₂OH) and 2.28 (1H, br s, OH).

INTERMEDIATE 12

3,5-Dichloro-4-bromomethylpyridine

A solution of Intermediate 11 (0.50g, 2.80mmol) in DCM (10ml) was treated with thionyl bromide (3.51g, 1.32ml, 16.9mmol) and heated to reflux for 3h. The reaction was quenched with 10% NaHCO₃ solution (10ml) and extracted with DCM (25ml). The organic layer was dried (MgSO₄) and concentrated *in vacuo* to give the title compound as a yellow oil that solidified on standing (0.65g, 96%) and was used without further purification. δ H (CDCl₃) 8.50 (2H, s, pyr-H), 4.63 (2H, s, CH₂Br). m/z (ESI, 60V) 242 (MH⁺).

EXAMPLE 1

N-(2,6-Dimethoxybenzoyl)-(O-benzyl)-L-tyrosine

Lithium hydroxide monohydrate (4.2mg, 1mmol) was added to a solution of Intermediate 1 (385mg, 0.857mmol) in THF (10ml) and water (10ml). The mixture was stirred for 1h at room temperature. The THF was removed under reduced pressure, the aqueous residue acidified (dilute HCl aq.) and extracted with DCM (3 x 50ml). The extracts were dried (Na₂SO₄) and evaporated under reduced pressure. The residue was freeze dried from a mixture of MeOH and water to give the title compound as a white fluffy solid (365mg, 98%). δ H (DMSO-d₆) 12.53 (1H, br s, CO₂H), 8.13 (1H, d, \downarrow 7.9Hz, CONH), 7.45-7.30 (5H, m, OCH₂Ph), 7.25 (1H, t, \downarrow 8.4Hz, Ar(OMe)H), 7.18 (2H, d, \downarrow 8.6Hz, CH₂Ar(O)H), 6.92 (2H, d, \downarrow 7.5Hz, CH₂Ar(O)H), 6.61 (2H, d, \downarrow 8.4Hz, Ar(OMe)H), 5.07 (2H, s, OCH₂Ph), 4.51 (1H, dt, \downarrow 5.1, 8.3Hz, CH α tyr), 3.63 (6H, s, 2 x Ar(OMe)), 3.00 (1H, dd, \downarrow

5.1, 14.0Hz, CHCH_AH_BAr) and 2.87 (1H, dd, \downarrow 8.6, 14.0Hz, CHCH_AH_BAr); m/z (ESI, 15V) 436 (MH⁺).

EXAMPLE 2

5 a) 2-Thio(S-4-methylphenyl)benzoyl-(O-2,6-dichlorobenzyl)-L-tyrosine

A solution of Intermediate 2 (0.24g, 0.41mmol) in THF (7.5ml) and water (4.5ml) was treated with lithium hydroxide monohydrate (26mg, 0.62mmol) and stirred at room temperature for 16h. The reaction was acidified to pH1
10 with 10% hydrochloric acid and extracted with DCM (2 x 20ml). The combined organic layers were dried over MgSO₄ and the solvent evaporated *in vacuo* to give a white solid which was triturated with EtOAc/hexane (1:1) to give the title compound (176mg, 76%). δ H (CDCl₃) 7.52 (1H, m), 7.34-7.14 (11H, m), 7.05 (1H, m), 6.90 (2H, m), 5.18 (2H, s),
15 5.04 (1H, m), 3.34 (1H, dd, \downarrow 5.6, 14.2Hz), 3.24 (1H, dd, \downarrow 5.7, 14.2Hz) and 2.34 (3H, s). m/z (ES⁺, 60V), 566 (MH⁺).

The following compounds were prepared in a similar manner from the corresponding esters produced in a similar manner to Intermediate 2:

20

b) (N-2-Chlorobenzoyl)-(O-2,6-dichlorobenzyl)-L-tyrosine

δ H (DMSO-d₆), 8.71 (1H, d, \downarrow 8.2Hz), 7.7-7.3 (7H, m), 7.23 (2H, d, \downarrow 8.4Hz), 6.97 (2H, d, \downarrow 8.4Hz), 4.58 (1H, m), 3.2-2.8 (2H, m). m/z 478 (MH⁺)

25

c) (N-2,4,6-Trimethylbenzoyl)-(O-2,6-dichlorobenzyl)-L-tyrosine

δ H (DMSO-d₆), 8.46 (1H, d, \downarrow 7.3Hz), 7.65-7.4 (3H, m), 7.25 (2H, d, \downarrow 8.6Hz), 6.95 (2H, d, \downarrow 8.6Hz), 6.76 (2H, s), 5.19 (2H, s), 4.65 (1H, m), 3.3-3.05 (1H, m), 2.95-2.75 (1H, m), 2.19 (3H, s) and 1.93 (6H, s); m/z (ESI,
30 60V) 486 (MH⁺).

d) (N-2,6-Dimethoxybenzoyl)-[O-(3,5-dichloro-4-pyridinyl)methyl]-L-tyrosine

The tyrosine starting material for coupling with acid to produce the required
35 ester for hydrolysis was obtained by reaction of Intermediate 12 with N-Boc-L-tyrosine methyl ester in the presence of sodium hydride.

δ H (DMSO- d_6), 12.55 (1H, br s, CO₂H), 8.72 (2H, s, pyr H), 8.15 (1H, d, \downarrow 7.8Hz, NH), 7.29-7.22 (3H, m, Ar-H), 6.98 (2H, d, \downarrow 8.6Hz, Ar-H), 6.63 (2H, d, \downarrow 8.6Hz, Ar-H), 5.21 (2H, s, CH₂O), 4.56 (1H, m, CH α), 3.65 (6H, s, OMe), 3.30-2.90 (2H, m, CHCH₂Ar); m/z (ESI, 60V) 505 (MH⁺).

5

e) *N*-2-Carboxybenzoyl-[O-(3,5-dichloro-4-pyridinyl)methyl]-L-tyrosine

δ H (DMSO- d_6), 12.8 (1H, br s, CO₂H), 8.72 (2H, s, pyr-H), 8.63 (1H, d, \downarrow 8.0Hz, NH), 7.72-7.69 (1H, m, Ar-H), 7.57-7.47 (2H, m, Ar-H), 7.31 (1H, m, Ar-H), 7.24 (2H, d, \downarrow 8.6Hz, Ar-H), 6.97 (2H, d, \downarrow 8.6Hz, Ar-H), 5.20 (2H, s, CH₂O), 4.55 (1H, m, CH α), 3.06-2.98 (2H, m, CHCH₂Ar); m/z (ESI, 60V) 489 (MH⁺).

10

EXAMPLE 3

15 a) 2-Carboxybenzoyl-(*N*'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine

Intermediate 4 (0.5g, 0.94mmol) was treated with lithium hydroxide monohydrate (0.095g, 2.26mmol) in dioxane/H₂O (30ml, 2:1). After 30min. glacial acetic acid was added (1ml) and the solvent removed *in vacuo*. Water was added to the residue and the white solid filtered, washed well with H₂O and dried *in vacuo* to give the title compound as a white solid (0.18g, 38%). δ H (DMSO- d_6) 10.84 (1H, s), 8.78 (2H, s), 8.68 (1H, d, \downarrow 7.2Hz), 7.71 (1H, dd), 7.58-7.50 (4H, m), 7.36-7.29 (3H, m), 4.61-4.56 (1H, m) and 3.13-2.98 (2H, m).

20

25

The following compounds were prepared in a similar manner from the corresponding ester. Each ester was prepared using a similar procedure to that described for the preparation of Intermediate 4, using (*N*-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine methyl ester hydrochloride [see Intermediate 4] and the appropriate activated acid:

30

b) [*N*-(6-Carboxy-2-methoxy)benzoyl]-(*N*-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine

δ H (DMSO- d_6), 10.85(1H, s, CO₂H), 8.77 (2H, s, ArCl₂H), 8.22 (2H, d, \downarrow 7.8Hz), 7.50-7.35 (2H, m), 7.35-7.20 (3H, m), 4.70-4.60 (1H, m, CH), 3.70 (3H, s, OMe), and 3.01 (2H, d, \downarrow 6.9Hz, CH₂); m/z (ESI, 60V) 532 (MH⁺).

35

- c) [N-(2-Phenoxy-6-carboxy)benzoyl]-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine
 5 δ H (DMSO-d⁶), 10.82 (1H, s, CO₂H), 8.77 (2H, s, ArCl₂H), 8.52 (1H, d, \downarrow 7.8Hz), 7.64 (1H, d, \downarrow 7.7Hz), 7.44 (2H, t, \downarrow 7.4Hz), 7.36 (2H, t, \downarrow 7.9Hz), 7.19 (2H, d, \downarrow 8.4Hz), 7.12 (2H, t, \downarrow 7.13Hz), 7.01 (2H, d, \downarrow 8.4Hz), 4.68-4.61 (1H, m, CH) and 2.96 (2H, d, \downarrow 6.2Hz, CH₂); m/z (ESI, 60V) 594 (MH⁺).
- 10 d) (N-2-Phenoxybenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine
 δ H (DMSO-d⁶), 10.78 (1H, br s, CO₂H), 8.77 (2H, s, ArCl₂H), 8.35 (1H, d, \downarrow 5.9Hz), 7.92 (1H, dd, \downarrow 7.8, 1.8Hz), 7.94-7.34 (6H, m, ArH), 7.21 (1H, t, \downarrow 7.5Hz), 7.15 (1H, t, \downarrow 7.2Hz), 7.02 (2H, d, \downarrow 8.6Hz), 6.95 (2H, d, \downarrow 8.6Hz),
 15 6.84 (1H, d, \downarrow 8.2Hz), 4.20-4.13 (1H, m, CH), 3.16 (1H, dd, \downarrow 13.0, 5.3Hz, CH_AH_B) and 3.01 (1H, dd, \downarrow 13.0, 4.3Hz, CH_AH_B); m/z (ESI, 60V) 550 (MH⁺).
- 20 e) [N-(2-Carboxy-6-methyl)benzoyl]-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine
 δ H (DMSO-d⁶), 8.78 (2H, s, ArCl₂H), 8.49 (1H, d, \downarrow 7.6Hz), 7.69 (1H, d, \downarrow 7.0Hz), 7.55 (2H, d, \downarrow 8.3Hz), 7.40-7.20 (4H, m), 4.72-4.60 (1H, m, CH), 3.11-2.93 (3H, m, Me) and 2.10 (2H, s, CH₂); m/z (ESI, 60V) 516 (MH⁺).
- 25 f) (N-2,6-Dimethoxybenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine
 δ H (DMSO-d⁶), 12.60 (1H, br s, NH), 10.86 (1H, s, NH), 8.79 (2H, s, pyr-H), 8.21 (1H, d, \downarrow 8.1Hz, Ar-H), 7.58 (2H, d, \downarrow 8.5Hz, Ar-H), 7.29 (2H, d, \downarrow 8.4Hz, Ar-H), 6.63 (2H, d, \downarrow 8.4Hz, Ar-H), 4.59 (1H, m, CH α), 3.66 (6H, s, OMe), 3.07 (1H, dd, \downarrow 13.8, 5.0Hz, CHCH_AH_BAr) and 2.92 (1H, dd, \downarrow 13.8, 9.0Hz, CHCH_AH_BAr); m/z (ESI, 60V) 518 (MH⁺).
- 30 g) (N-3-Carboxybenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine
 δ H (DMSO-d⁶), 12.95 (1H, br s, CO₂H), 10.83 (1H, s, NH), 8.95 (1H, d, \downarrow 8.1Hz, Ar-H), 8.77 (2H, s, pyr-H), 8.43 (1H, t, \downarrow 1.6Hz, Ar-H), 8.06 (2H, m,

Ar-H), 7.60 (1H, m, Ar-H), 7.55 (2H, d, \downarrow 8.5Hz, Ar-H), 7.32 (2H, d, \downarrow 8.5Hz, Ar-H), 4.64 (1H, m, CH α) and 3.10 (2H, m, CHCH₂Ar); m/z (ESI, 160V) 502 (MH⁺).

5 h) (N-4-Carboxybenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine

8H (DMSO-d₆, 350K), 12.62 (1H, br s, CO₂H), 10.60 (1H, s, NH), 8.72 (2H, s, pyr-H), 8.56 (1H, d, \downarrow 7.9Hz, NH), 8.01 (2H, d, \downarrow 8.4Hz, Ar-H), 7.88 (2H, d, \downarrow 8.4Hz, Ar-H), 7.55 (2H, d, \downarrow 8.4Hz, Ar-H), 7.31 (2H, d, \downarrow 8.4Hz, Ar-H), 4.70 (1H, m, CH α), 3.22 (1H, dd, \downarrow 14.0, 5.0Hz, CHCH_AH_BAr) and 3.11 (1H, dd, \downarrow 14.0, 9.5Hz, CHCH_AH_BAr); m/z (ESI, 160V), 502 (MH⁺).

i) (N-2-Carboxy-6-hydroxybenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine

15 8H (DMSO-d₆), 10.84 (1H, s, NH), 8.87 (2H, s, pyr-H), 8.52 (1H, d, \downarrow 8.0Hz, Ar-H), 7.56 (2H, d, \downarrow 8.3Hz, Ar-H), 7.29-7.26 (3H, m, Ar-H), 6.94 (1H, d, \downarrow 8.3Hz, Ar-H), 6.85 (1H, d, \downarrow 8.3Hz, Ar-H), 4.454 (1H, m, CH α), 3.16-2.96 (2H, m, CHCH₂Ar); m/z (ESI, 60V) 518 (MH⁺).

20 j) (N-2-t-Butoxycarbonylbenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine

25 8H (DMSO-d₆), 10.84 (1H, s, NH), 8.78 (2H, s, pyr-H), 8.62 (1H, m, NH), 7.64-7.44 (5H, m, Ar-H), 7.39-7.20 (3H, m, Ar-H), 4.56 (1H, m, CH α), 3.16 (1H, m, CHCH_AH_BS), 3.09-2.94 (1H, m, CHCH_AH_BAr) and 1.36 (9H, s, ^tBu); m/z (ESI, 60V) 580 (MH⁺).

EXAMPLE 4

a) (N-2,6-Dimethoxybenzoyl)-4-(carboxamidobenzyl)phenylalanine

A solution of Intermediate 9 (1.07g, 1.82mmol) in 1,4-dioxane (100ml) was treated with lithium hydroxide (168mg, 4.0mmol) and water (20ml). The reaction was stirred at room temperature for 2h then THF (50ml) was added and stirring continued for a further 1h. The reaction was concentrated *in vacuo* and the residue partitioned between EtOAc (50ml) and water (50ml). The aqueous layer was washed with EtOAc (50ml) and the combined organic layers extracted with water (100ml). The combined aqueous layers were acidified to pH 1 with 2.0M hydrochloric acid and

extracted with EtOAc (3 x 50ml). The combined organic layers were dried (Na₂SO₄) and concentrated *in vacuo* to give a white solid (0.96g) which was purified by crystallisation from EtOAc/diisopropyl ether to give the title compound as a white solid (0.56g, 66%). δ H (DMSO-d₆) 8.99 (1H, t, \downarrow 6.0Hz, NH), 8.24 (1H, d, \downarrow 8.0Hz, NH), 7.84 (2H, d, \downarrow 8.3, Ar-H), 7.38 (2H, d, \downarrow 8.3Hz, Ar-H), 7.33-7.30 (5H, m, Ar-H), 7.26 (1H, t, \downarrow 8.4Hz, Ar-H), 6.63 (2H, d, \downarrow 8.4Hz, Ar-H), 4.62 (1H, m, CH α), 4.48 (2H, d, \downarrow 6.0Hz, NHCH₂Ph), 3.64 (6H, s, OMe), 3.13 (1H, dd, \downarrow 14.0, 4.9Hz, CHCH_AH_BAr) and 2.99 (1H, dd, \downarrow 14.0, 9.0Hz, CHCH_AH_BAr). m/z (ESI, 60V) 463 (MH⁺).

The following compounds were prepared in a similar manner to the compound of Example 4a) by hydrolysis of the corresponding ester. Each ester was prepared by reaction of Intermediate 8 with the amine shown using a similar procedure to that described for the preparation of Intermediate 9.

b) (N-2,6-Dimethoxybenzoyl)-4-[carboxamido(3,5-dichlorobenzyl)]-phenylalanine

from Intermediate 8 and 3,5-dichloroaniline. δ H (DMSO-d₆, 390K), 10.46 (1H, s, NH), 8.27 (1H, d, \downarrow 8.0Hz, NH), 7.91 (2H, d, \downarrow 1.9Hz, Ar-H), 7.89 (2H, d, \downarrow 8.3Hz, Ar-H), 7.46 (2H, d, \downarrow 8.3Hz, Ar-H), 7.31 (1H, t, \downarrow 1.9Hz, Ar-H), 7.26 (1H, t, \downarrow 8.4Hz, Ar-H), 6.63 (2H, d, \downarrow 8.4Hz, Ar-H), 4.64 (1H, m, CH α), 3.65 (6H, s, OMe), 3.17 (1H, dd, \downarrow 14.0, 5.1Hz, CHCH_AH_BAr), and 3.03 (1H, dd, \downarrow 14.0, 9.0Hz, CHCH_AH_BAr). m/z (ESI, 60V) 518 (MH⁺).

c) (N-2,6-Dimethoxybenzoyl)-4-(carboxamidomorpholyl)-phenylalanine

from Intermediate 8 and morpholine. δ H (DMSO-d₆, 390K), 8.26 (1H, d, \downarrow 7.9Hz, NH), 7.34 (4H, m, Ar-H), 7.26 (1H, t, \downarrow 8.4Hz), 6.62 (2H, d, \downarrow 8.4Hz, Ar-H), 4.61 (1H, m, CH α), 3.81-3.40 (8H, m, CH₂), 3.64 (6H, s, OMe), 3.11 (1H, dd, \downarrow 13.9, 4.75Hz, CHCH_AH_BAr) and 2.98 (1H, dd, \downarrow 13.9, 9.0Hz, CHCH_AH_BAr). m/z (ESI, 60V) 443 (MH⁺)

d) (N-2,6-Dimethoxybenzoyl)-4-(carboxamidodiethyl)phenylalanine
from Intermediate 8 and diethylamine δ H (DMSO-d₆), 8.24 (1H, d, \downarrow 8.0Hz, NH), 7.32 (5H, m, Ar-H), 6.63 (2H, d, \downarrow 8.4Hz, Ar-H), 4.61 (1H, m,

CH α), 4.11 (4H, m, CH₂CH₃), 3.65 (6H, s, OMe), 3.34-2.99 (2H, m, CHCH₂Ar) and 1.08 (6H, t, \downarrow 7.1Hz, CH₂CH₃). m/z (ESI, 60V) 429 (MH⁺)

EXAMPLE 5

5 **[N-(4-Phenyl)benzoyl]-[O-(3,5-dichloro-4-pyridinyl)methyl]-L-tyrosine**

To 4-phenylbenzoyl-L-tyrosine (0.75g, 2mmol) and DMF (20ml) in a flask under N₂ was added 2.1 equivalents of a 60% dispersion of NaH (0.168g). This mixture was stirred at room temperature for 20 minutes followed by the addition of Intermediate 12 (0.484g, 2mmol). Stirring was continued for
10 2.5h. The reaction was then quenched with aqueous NaHCO₃, the DMF was evaporated, EtOAc and water were added and a white solid appeared which was filtered and washed with water and Et₂O. The white solid was passed through a Dowex-56WX4-400 ion exchange resin, eluting with THF/acetonitrile [50:50] and freeze dried to afford the title compound as a
15 white solid (0.3g). δ H (DMSO-d₆), 8.7 (2H, s), 7.95-7.35 (10H, m), 7.1 (2H, d, \downarrow 8.5Hz), 6.85 (2H, d, \downarrow 8.5Hz), 5.15 (2H, s), 4.15 (1H, br s) and 3.31-3.05 (2H, m). m/z 521 (MH⁺)

EXAMPLE 6

20 **(N-3-Cyanobenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine**

To Intermediate 4b) (0.174g, 0.35mmol) in THF (5ml) and water (5ml) was added lithium hydroxide monohydrate (22mg). The reaction was stirred at room temperature for 3h. The THF was evaporated, the pH adjusted to 4
25 and the solution extracted with EtOAc, dried over MgSO₄, filtered and evaporated to afford the title compound as an off-white solid (0.137g, 81%). δ H (CD₃OD), 8.55 (2H, s), 8.15-7.35 (6H, m), 7.25 (2H, d, \downarrow 7.02Hz), 4.97 (1H, m) and 3.25-3.13 (2H, m). m/z (ES) 483 (MH⁺).

30 **EXAMPLE 7**

[N-3-(1-H-Tetrazol-5-yl)]-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine

To Intermediate 10 (0.214g, 0.396mmol) in MeOH (5ml) and water (5ml) was added lithium hydroxide monohydrate (25mg) and the reaction stirred
35 at room temperature for 3h. The MeOH was evaporated and the pH was adjusted to 6.5 using 1M hydrochloric acid. A white solid appeared, which

was filtered and washed with EtOAc. The solid was then passed through a Dowex-50WX4-400 ion exchange column eluting with CH₃CN/water (50:50) to afford the title compound as a white solid (0.088g, 42%). δ H (CD₃OD) 8.60 (2H, s), 8.40 (1H, s), 8.15 (1H, d, \downarrow 7.8Hz), 7.9 (1H, d, \downarrow 7.8Hz), 7.68-7.51 (3H, m), 7.3 (2H, d, \downarrow 8.5Hz), 4.95-4.85 (1H, m) and 3.39-3.08 (2H, m). m/z (ES) 526 (MH⁺).

EXAMPLE 8

[(N-(3-Methoxycarbonylbenzoyl))-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenyl]alnine

To Intermediate 4c) (0.39g) in dry DCM (5ml) was added trifluoroacetic acid (1ml) and the reaction stirred for 3h. Further trifluoroacetic acid (1.5ml) and DCM (5ml) were added and the reaction stirred for a total of 6h. The mixture was evaporated, acetonitrile/water was added and freeze drying afforded the title compound as a white solid (0.257g, 60%). δ H (CD₃OD), 8.61 (2H, s), 7.85-7.03 (8H, m), 4.89 (1H, m), 3.69 (3H, s) and 3.1-3.0 (2H, m). m/z (ES) 516 (MH⁺).

The following assays can be used to demonstrate the potency and selectivity of the compounds according to the invention. In each of these assays an IC₅₀ value was determined for each test compound and represents the concentration of compound necessary to achieve 50% inhibition of cell adhesion where 100% = adhesion assessed in the absence of the test compound and 0% = absorbance in wells that did not receive cells.

$\alpha_4\beta_1$ Integrin-dependent Jurkat cell adhesion to VCAM-Ig

96 well NUNC plates were coated with F(ab)₂ fragment goat anti-human IgG Fc γ -specific antibody [Jackson Immuno Research 109-006-098: 100 μ l at 2 μ g/ml in 0.1M NaHCO₃, pH 8.4], overnight at 4°. The plates were washed (3x) in phosphate-buffered saline (PBS) and then blocked for 1h in PBS/1% BSA at room temperature on a rocking platform. After washing (3x in PBS) 9 ng/ml of purified 2d VCAM-Ig diluted in PBS/1% BSA was added and the plates left for 60 minutes at room temperature on a rocking platform. The plates were washed (3x in PBS) and the assay then

performed at 37° for 30 min in a total volume of 200 μ l containing 2.5×10^5 Jurkat cells in the presence or absence of titrated test compounds.

Each plate was washed (2x) with medium and the adherent cells were
5 fixed with 100 μ l methanol for 10 minutes followed by another wash. 100 μ l 0.25% Rose Bengal (Sigma R4507) in PBS was added for 5 minutes at room temperature and the plates washed (3x) in PBS. 100 μ l 50% (v/v) ethanol in PBS was added and the plates left for 60min after which the absorbance (570nm) was measured.

10

$\alpha_4\beta_7$ Integrin-dependent JY cell adhesion to MAdCAM-Ig

This assay was performed in the same manner as the $\alpha_4\beta_1$ assay except that MAdCAM-Ig (150ng/ml) was used in place of 2d VCAM-Ig and a sub-line of the β -lympho blastoid cell-line JY was used in place of Jurkat cells.

15 The IC₅₀ value for each test compound was determined as described in the $\alpha_4\beta_1$ integrin assay.

$\alpha_5\beta_1$ Integrin-dependent K562 cell adhesion to fibronectin

96 well tissue culture plates were coated with human plasma fibronectin
20 (Sigma F0895) at 5 μ g/ml in phosphate-buffered saline (PBS) for 2 hr at 37°C. The plates were washed (3x in PBS) and then blocked for 1h in 100 μ l PBS/1% BSA at room temperature on a rocking platform. The blocked plates were washed (3x in PBS) and the assay then performed at 37°C in a total volume of 200 μ l containing 2.5×10^5 K562 cells, phorbol-12-
25 myristate-13-acetate at 10ng/ml, and in the presence or absence of titrated test compounds. Incubation time was 30 minutes. Each plate was fixed and stained as described in the $\alpha_4\beta_1$ assay above.

30 **$\alpha_m\beta_2$ -dependent human polymorphonuclear neutrophils adhesion to plastic**

96 well tissue culture plates were coated with RPMI 1640/10% FCS for 2h at 37°C. 2×10^5 freshly isolated human venous polymorphonuclear neutrophils (PMN) were added to the wells in a total volume of 200 μ l in the presence of 10ng/ml phorbol-12-myristate-13-acetate, and in the presence
35 or absence of test compounds, and incubated for 20min at 37°C followed by 30min at room temperature. The plates were washed in medium and

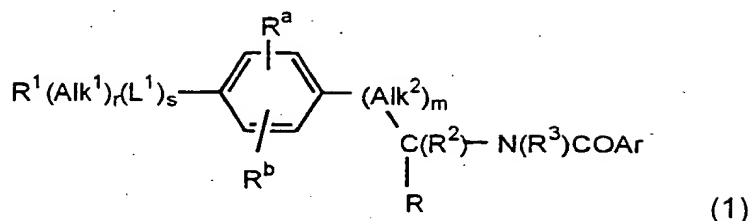
- 100 μ l 0.1% (w/v) HMB (hexadecyl trimethyl ammonium bromide, Sigma H5882) in 0.05M potassium phosphate buffer, pH 6.0 added to each well. The plates were then left on a rocker at room temperature for 60 min. Endogenous peroxidase activity was then assessed using tetramethyl benzidine (TMB) as follows: PMN lysate samples mixed with 0.22% H₂O₂ (Sigma) and 50 μ g/ml TMB (Boehringer Mannheim) in 0.1M sodium acetate/citrate buffer, pH 6.0 and absorbance measured at 630nm.

α IIb/ β ₃ -dependent human platelet aggregation

- 10 Human platelet aggregation was assessed using impedance aggregation on the Chronolog Whole Blood Lumiaggregometer. Human platelet-rich plasma (PRP) was obtained by spinning fresh human venous blood anticoagulated with 0.38% (v/v) tri-sodium citrate at 220xg for 10 min and diluted to a cell density of 6 x 10⁸/ml in autologous plasma. Cuvettes
- 15 contained equal volumes of PRP and filtered Tyrode's buffer (g/liter: NaCl 8.0; MgCl₂.H₂O 0.427; CaCl₂ 0.2; KCl 0.2; D-glucose 1.0; NaHCO₃ 1.0; NaHPO₄.2H₂O 0.065). Aggregation was monitored following addition of 2.5 μ M ADP (Sigma) in the presence or absence of inhibitors.
- 20 In the above assays the compounds of the invention generally have IC₅₀ values in the α ₄ β ₁ and α ₄ β ₇ assays of 1 μ M and below. Compounds of the Examples typically had IC₅₀ values of 100nM and below in these assays and demonstrated selective inhibition of α ₄ β ₁. In the other assays featuring α integrins of other subgroups the same compounds had IC₅₀
- 25 values of 50 μ M and above thus demonstrating the potency and selectivity of their action against α ₄ integrins.

CLAIMS

1. A compound of formula (1):



5

wherein

R is a carboxylic acid or a derivative thereof;

10 R¹ is a hydrogen atom or a hydroxyl, straight or branched alkoxy or optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

Alk¹ is an optionally substituted aliphatic or heteroaliphatic chain;

L¹ is a linker atom or group;

15 r and s, which may be the same or different, is each zero or an integer 1 provided that when r is zero R¹ is an optionally substituted cycloaliphatic, polycycloaliphatic, heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic group;

20 R^a and R^b, which may be the same or different is each an atom or group -L²(CH₂)_pL³(R^c)_q in which L² and L³ is each a covalent bond or a linker atom or group, p is zero or the integer 1, q is an integer 1, 2 or 3 and R^c is a hydrogen or halogen atom or a group selected from straight or branched alkyl, -OR^d [where R^d is a hydrogen atom or an optionally substituted straight or branched alkyl group], -SR^d, -NR^dR^e, [where R^e is as just defined for R^d and may be the same or different], -NO₂, -CN, -CO₂R^d, 25 -SO₃H, -SO₂R^d, -OCO₂R^d, -CONR^dR^e, -OCONR^dR^e, -CSNR^dR^e, -COR^d, -N(R^d)COR^e, N(R^d)CSR^e, -SO₂N(R^d)(R^e), -N(R^d)SO₂R^e, -N(R^d)CONR^eR^f [where R^f is a hydrogen atom or an optionally substituted straight or branched alkyl group], -N(R^d)CSNR^eR^f or -N(R^d)SO₂NR^eR^f;

Alk² is a straight or branched alkylene chain;

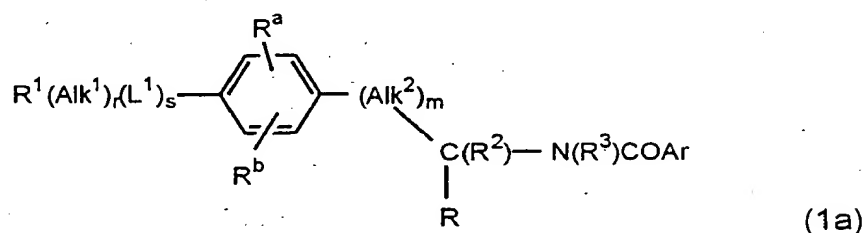
30 m is zero or an integer 1;

R² is a hydrogen atom or a methyl group;

R³ is a hydrogen atom or a straight or branched alkyl group;

Ar is an optionally substituted aromatic group;
and the salts, solvates, hydrates and N-oxides thereof for use in
modulating cell adhesion.

- 5 2. A compound of formula (1a):

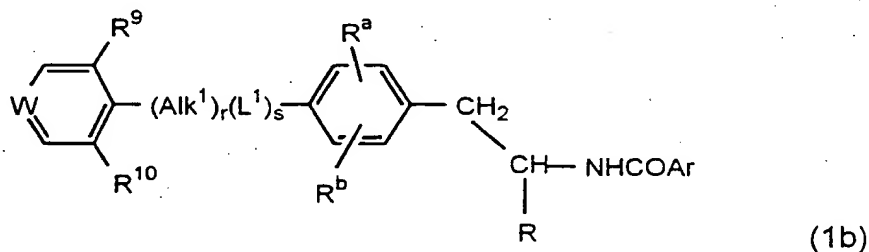


wherein

- 10 R is a carboxylic acid or a derivative thereof;
R¹ is an optionally substituted cycloaliphatic, polycycloaliphatic,
heterocycloaliphatic, polyheterocycloaliphatic, aromatic or heteroaromatic
group;
Alk¹ is an optionally substituted aliphatic or heteroaliphatic chain;
15 L¹ is a linker atom or group;
r and s, which may be the same or different, is each zero or an integer 1;
R^a and R^b, which may be the same or different is each an atom or group
-L²(CH₂)_pL³(R^c)_q in which L² and L³ is each a covalent bond or a linker
atom or group, p is zero or the integer 1, q is an integer 1, 2 or 3 and R^c is
20 a hydrogen or halogen atom or a group selected from straight or branched
alkyl, -OR^d [where R^d is a hydrogen atom or an optionally substituted
straight or branched alkyl group], -SR^d, -NR^dR^e, [where R^e is as just
defined for R^d and may be the same or different], -NO₂, -CN, -CO₂R^d,
-SO₃H, -SO₂R^d, -OCO₂R^d, -CONR^dR^e, -OCONR^dR^e, -CSNR^dR^e, -COR^d,
25 -N(R^d)COR^e, N(R^d)CSR^e, -SO₂N(R^d)(R^e), -N(R^d)SO₂R^e, -N(R^d)CONR^eR^f
[where R^f is a hydrogen atom or an optionally substituted straight or
branched alkyl group], -N(R^d)CSNR^eR^f or -N(R^d)SO₂NR^eR^f;
Alk² is a straight or branched alkylene chain;
m is zero or an integer 1;
30 R² is a hydrogen atom or a methyl group;
R³ is a hydrogen atom or a straight or branched alkyl group;
Ar is an optionally substituted aromatic group;

and the salts, solvates, hydrates and N-oxides thereof.

3. A compound according to Claim 2 wherein Ar is an optionally substituted phenyl group.
- 5 4. A compound according to Claim 2 or Claim 3 wherein R is a $-\text{CO}_2\text{H}$ group.
- 10 5. A compound according to any of Claim 2 to Claim 4 wherein Alk^2 is a $-\text{CH}_2-$ chain and m is an integer 1.
6. A compound according to any of Claim 2 to Claim 5 wherein each of R^2 and R^3 is a hydrogen atom.
- 15 7. A compound according to any one of Claim 2 to Claim 6 wherein R^1 is an optionally substituted aromatic or heteroaromatic group.
8. A compound according to Claim 7 wherein R^1 is an optionally substituted phenyl, pyridyl or pyrimidinyl group.
- 20 9. A compound according to any one of Claim 2 to Claim 8 wherein $-(\text{Alk}^1)_r(\text{L}^1)_s$ is a $-\text{CH}_2\text{O}-$, $-\text{SO}_2\text{NH}-$, $-\text{C}(\text{O})\text{O}-$ or $-\text{CON}(\text{R}^4)-$ group.
10. A compound according to Claim 9 wherein $-(\text{Alk}^1)_r(\text{L}^1)_s$ is a
- 25 $-\text{CONH}-$ group.
11. A compound according to Claim 2 which has the formula (1b):



wherein -W= is -CH= or -N=, R^9 and R^{10} , which may be the same or different is each a $-L^2(CH_2)_pL^3(R^c)_q$ atom or group, and the salts, solvates, hydrates and N-oxides thereof.

5 12. A compound according to Claim 11 wherein Ar is an optionally substituted phenyl group.

13. A compound which is:

- (N-2,6-Dimethoxybenzoyl)-[O-(3,5-dichloro-4-pyridinyl)methyl]-L-tyrosine;
 10 2-Carboxybenzoyl-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
 (N-2,6-Dimethoxybenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
 (N-3-Carboxybenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
 15 (N-4-Carboxybenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
 (N-2-t-Butoxycarbonylbenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
 (N-3-Cyanobenzoyl)-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
 20 [N-3-(1-H-Tetrazol-5-yl)]-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
 [N-(3-Methoxycarbonylbenzoyl)]-(N'-3,5-dichloroisonicotinoyl)-L-4-aminophenylalanine;
 25 and the salts, solvates, hydrates and N-oxides thereof.

14. A pharmaceutical composition comprising a compound according to Claim 1 together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/00589

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C235/60 C07C233/87 C07C237/30 C07D295/18 C07D213/61
C07D213/81 A61K31/195 A61K31/455

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 10312 A (F. HOFFMANN-LA ROCHE) 4 March 1999 see claims 1,35-43; examples ---	1-10,14
X	WO 97 36859 A (G.D. SEARLE & CO.) 9 October 1997 see page 1, line 1 - page 16, line 16; claims; examples 36,47 ---	1-10,14
X	EP 0 710 657 A (MERCK) 8 May 1996 see page 18, line 14 - line 22 see page 18, line 51 - line 54; claims --- -/--	1,2

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

9 June 1999

Date of mailing of the international search report

25/06/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Zervas, B

INTERNATIONAL SEARCH REPORT

Int. l. Application No
PCT/GB 99/00589

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GUILLERMO TOUS ET AL.: "O'-(Epoxyalkyl)tyrosines and (Epoxyalkyl)phenylalanine as Irreversible Inactivators of Serine Proteases: Synthesis and Inhibition Mechanism" JOURNAL OF MEDICINAL CHEMISTRY., vol. 33, no. 6, June 1990, pages 1620-1634, XP002105436 WASHINGTON US see page 1629, column 1, line 10 - line 40 see page 1629, column 1, line 62 - column 2, line 2 see page 1629, column 2, line 21 - line 45 see page 1630, column 2, line 36 - line 55 see page 1631, column 1, line 3 - line 21 see page 1631, column 2, line 3 - line 48</p>	1,2,14
X	<p>US 4 470 973 A (E.R. SQUIBB & SONS) 11 September 1984 see column 25, line 59 - column 26, line 2</p>	1-9
X	<p>AIDA EL AZZOUNY ET AL.: "Zur Synthese. acyclischer und cyclischer Anthranilsäure-Phenylalanin-Peptide" PHARMAZIE., vol. 32, no. 6, 1977, pages 318-323, XP002105437 BERLIN DD see page 319, column 1, table, compounds 6, 9, 13</p>	1-9
X	<p>A. BADSHAH ET AL.: "Catalytic Reduction of Azlactones in Alkaline Media: Synthesis of Amino Acids" JOURNAL OF ORGANIC CHEMISTRY., vol. 37, no. 18, September 1972, pages 2916-2918, XP002105438 EASTON US see page 2917, table II, compound with the registry no. 34996-89-9</p>	1
A	<p>WO 98 00395 A (MERCK) 8 January 1998 see claims; examples</p>	1,14
P,A	<p>WO 98 54207 A (CELLTECH THERAPEUTICS) 3 December 1998 see claims; examples</p>	1,14

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Information on patent family members

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Information on patent family members

International Application No

PCT/GB 99/00589

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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